IN THE THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

PHARMACIA & UPJOHN COMPANY LLC, Plaintiff, v. MAYNE PHARMA (USA) INC., Defendant.	C.A. No. _____

COMPLAINT

Plaintiff Pharmacia & Upjohn Company LLC alleges a claim for patent infringement against Defendant Mayne Pharma (USA) Inc., as follows:

THE PARTIES

1. Plaintiff Pharmacia & Upjohn Company LLC ("Pharmacia") is a Delaware corporation having a principal place of business at 7000 Portage Road, Kalamazoo, MI 49001. Pharmacia is part of Pfizer Inc., which is engaged in the business of researching, developing, making, and selling pharmaceutical products for the human healthcare market.

2. On information and belief, Defendant Mayne Pharma (USA) Inc. ("Mayne") is a Delaware corporation having a principal place of business at 650 From Road, Mack-Cali Centre II, Second Floor, Paramus, NJ 07652. Mayne is engaged in the business of making and selling generic injectable pharmaceutical products for the human healthcare market.

JURISDICTION AND VENUE

3. This is an action under the Patent Act, 35 U.S.C. § 1 *et seq.*, and the Declaratory Judgment Act, 28 U.S.C. § 2201 *et* seq., to obtain a judgment of patent infringement. The jurisdiction of this Court is properly founded under 28 U.S.C. §§ 1331 and 1338(a).

4. Venue in this Court is proper under 28 U.S.C. §§ 1391 and § 1400(b).

5. Mayne received tentative approval from the U.S. Food and Drug Administration ("FDA") to market its generic epirubicin hydrochloride product on August 17, 2006. On information and belief, Mayne will begin to distribute, market, and sell that product imminently throughout the United States, including in this State and this judicial district. For at least the reasons set forth above, Mayne is subject to personal jurisdiction in this judicial district.

THE PATENT-IN-SUIT

6. Epirubicin hydrochloride belongs to a class of chemotherapy drugs known as anthracycline glycosides. Other frequently prescribed chemotherapy drugs in this class include doxorubicin hydrochloride and idarubicin hydrochloride. Different anthracycline glycosides are prescribed for different oncology indications, and are not used interchangeably by the medical community.

7. Pharmacia is the owner of U.S. Patent No. 6,107,285 ("the '285 patent"), entitled "Injectable Ready-To-Use Solutions Containing An Antitumor Anthracycline Glycoside" (attached as Exhibit A), which is a valid patent, legally issued on August 22, 2000.

8. Anthracycline glycosides must be administered to patients via injection, i.e., they cannot be administered orally. Prior to this invention, anthracycline glycosides were understood to be unstable in solution. As a result of such instability, anthracycline glycosides were

previously made, sold, and distributed in a dosage form of a lyophilized powder that had to be reconstituted by medical personnel before administration to the patient.

9. Anthracycline glycosides are extremely toxic, even to the touch. Prior to this invention, medical personnel were frequently exposed to droplets of anthracycline glycoside solutions during the process of reconstituting the lyophilized powder. Such contact with anthracycline glycosides created a significant health risk for the medical workers in this field.

10. As a result, there was a strong desire among medical workers in the chemotherapy community for a dosage form of anthracycline glycoside, including epirubicin hydrochloride, that had long term storage properties in a ready-to-use injection solution. The present invention represents the first successful solution of that situation.

The Infringing Conduct By Defendant

11. On August 17, 2006, the FDA granted tentative approval to Mayne to market its Epirubicin Hydrochloride Injection product under NDA #050807. On information and belief, Mayne's approval to market its Epirubicin Hydrochloride Injection product will become final on September 15, 2006, the date of the expiration of Pharmacia's orphan drug exclusivity.

12. On information and belief, Mayne intends to import, sell, and offer to sell Epirubicin Hydrochloride Injection product for treating patients, and also to induce others to sell and use the infringing product. On information and belief, the Epirubicin Hydrochloride Injection product soon to be imported and sold by Mayne is formulated in a solution ready-to-use for intravenous injection.

13. Mayne's Epirubicin Hydrochloride Injection product falls within the scope of one or more of the claims of the '285 patent.

14. On information and belief, Mayne intends to commit these acts with full knowledge of the '285 patent, and with deliberate disregard for Pharmacia's rights in that patent.

15. Mayne is well aware of the family of patents to which the '285 patent belongs, having previously attempted unsuccessfully to bring its epirubicin hydrochloride product into other countries outside the United States. For example, Mayne was found to have infringed a related United Kingdom patent in *Mayne Pharma Pty Limited v. Pharmacia Italia S.p.A* (attached as Exhibit B). Mayne was also found to have infringed the Australian counterpart to the '285 patent in *Pharmacia Italia S.p.A v. Mayne Pharma Pty Ltd.* (attached as Exhibit C). And Mayne was barred from marketing its epirubicin hydrochloride product in Canada in *Pfizer Canada Inc. v. Minister of Health* (attached as Exhibit D).

Count I - Patent Infringement Under 35 U.S.C. § 271(e)(2)

16. Pharmacia re-alleges and incorporates by reference paragraphs 1-15.

17. Mayne has previously filed New Drug Application, NDA #050807, for epirubicin hydrochloride, with the FDA.

18. On information and belief, Mayne submitted this application under § 505(b)(2) of the Federal Food, Drug and Cosmetic Act.

19. On information and belief, Mayne's epirubicin hydrochloride product falls within the scope of one or more claims of the '285 patent.

20. By submitting its application under § 505(b)(2) of the Federal Food, Drug and Cosmetic Act, Mayne has infringed the '285 patent under 35 U.S.C. § 271 (e)(2).

Count II – Declaratory Judgment Of Direct Infringement Of Patent Infringement Of The '285 Patent

21. Pharmacia re-alleges and incorporates by reference paragraphs 1-15, and 17-20.

22. Mayne intends to engage imminently in the importation, offer for sale, and sale of its epirubicin hydrochloride product. When it does so, Mayne will infringe the '285 patent under 35 U.S.C. § 271(a).

23. Mayne's actions will constitute willful infringement of Pharmacia's patent rights under 35 U.S.C. § 284.

24. On information and belief, the acts of Mayne will continue unless and until enjoined by this Court.

Count III – Declaratory Judgment Of Inducement Of Patent Infringement Of The '285 Patent

25. Pharmacia re-alleges and incorporates by reference paragraphs 1-15, 17-20, and 22-24.

26. On information and belief, Mayne will actively be inducing others to distribute, sell, offer for sale, and use its epirubicin hydrochloride product that is covered by one or more claims of the '285 patent as described above.

27. In view of these facts, Mayne will be actively inducing infringement of the '285 patent in violation of 35 U.S.C. § 271(b).

28. Mayne's actions will constitute willful infringement of Pharmacia's patent rights under 35 U.S.C. § 284.

29. On information and belief, the acts of Mayne will continue unless and until enjoined by this Court.

Count IV – Declaratory Judgment Of
Contributory Infringement Of The '285 Patent

30. Pharmacia re-alleges and incorporates by reference paragraphs 1-15, 17-20, 22-24, and 26-29.

31. On information and belief, Mayne will imminently be importing, selling, and offering to sell its epirubicin hydrochloride product, which constitutes a material part of the invention claimed in the '285 patent, knowing it to be especially made or adapted for use in an infringement of one or more claims of the '285 patent as described above, and not a staple article or commodity of commerce suitable for substantial noninfringing uses.

32. In view of these facts, Mayne will be contributorily infringing the '285 patent in violation of 35 U.S.C. § 271 (c).

33. Mayne's actions will constitute willful infringement of Pharmacia's patent rights under 35 U.S.C. § 284.

34. On information and belief, the acts of Mayne will continue unless and until enjoined by this Court.

RELIEF REQUESTED

WHEREFORE, Plaintiff Pharmacia prays for judgment and relief including:

(A) Judgment that Mayne has infringed United States Patent No. 6,107,285 under 35 U.S.C. § 271(e)(2);

(B) A Declaratory Judgment that Mayne will directly infringe, will induce infringement and will contributorily infringe of one or more claims of United States Patent No. 6,107,285 under 35 U.S.C. § 271(a), (b), and (c) by making, using, offering to sell, and selling its epirubicin hydrochloride product in the manner explained above;

(C) A preliminary and permanent injunction, enjoining Mayne and its officers, agents, servants, employees, privies, and others acting for, on behalf of, or in concert with any of them from making, using, selling, and offering to sell epirubicin hydrochloride and thus infringing or inducing infringement of any of the claims of United States Patent No. 6,107,285;

(D) An Order directing Mayne to recall all stocks of its infringing epirubicin hydrochloride product remaining in the hands of commercial distributors and resellers;

(E) An Order directing Mayne to destroy any stocks of its infringing epirubicin hydrochloride product;

(F) An Order awarding to Pharmacia damages adequate to compensate for the infringement, including lost profits past and future, but in no event less than a reasonable royalty for the use made of the invention by Mayne;

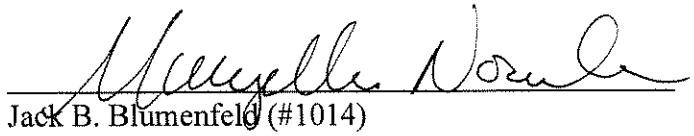
(G) An award of increased damages pursuant to 35 U.S.C. § 284;

(H) An award declaring this case exceptional pursuant to 35 U.S.C. § 285 and granting Pharmacia its attorneys fees in this case;

(I) An award of costs and interest against Mayne; and

(J) Such other and further equitable relief as this Court may deem just and proper.

MORRIS, NICHOLS, ARSHT & TUNNELL LLP



Jack B. Blumenfeld (#1014)
Maryellen Noreika (#3208)
1201 N. Market Street
P.O. Box 1347
Wilmington, DE 19899
(302) 658-9200
Attorneys for Plaintiff
Pharmacia & Upjohn Company LLC

OF COUNSEL:

Daniel A. Boehnen
Grantland G. Drutchas
Joshua R. Rich
Nicole Keenan
McDonnell Boehnen Hulbert & Berghoff LLP
300 S. Wacker Drive
Chicago, IL 60606
(312) 913-0001

September 7, 2006

EXHIBIT A

US006107285A

United States Patent [19]

Gatti et al.

[11] Patent Number: 6,107,285

[45] Date of Patent: *Aug. 22, 2000

[54] INJECTABLE READY-TO-USE SOLUTIONS CONTAINING AN ANTITUMOR ANTHRACYCLINE GLYCOSIDE

[75] Inventors: **Gaetano Gatti**, Sesto San Giovanni; **Diego Oldani**, Robecco sul Naviglio; **Giuseppe Bottoni**, Bergamo; **Carlo Confalonieri**, Cusano Milanino; **Luciano Gambini**, Cornaredo; **Roberto De Ponti**, Milan, all of Italy

[73] Assignee: **Pharmacia & UpJohn Company**, Kalamazoo, Mich.

[*] Notice: This patent is subject to a terminal disclaimer.

[21] Appl. No.: **07/827,742**

[22] Filed: **Jan. 29, 1992**

Related U.S. Application Data

[62] Division of application No. 07/503,856, Apr. 3, 1990, Pat. No. 5,124,317.

[30] **Foreign Application Priority Data**

Aug. 2, 1985 [GB] United Kingdom 8519452

[51] **Int. Cl.**[7] **A61K 31/70**

[52] **U.S. Cl.** **514/34**; 536/6.4

[58] **Field of Search** 536/6.4, 34; 424/78; 514/34

[56] **References Cited**

U.S. PATENT DOCUMENTS

3,590,028	6/1971	Arcamone et al. .	
3,686,163	8/1972	Arcamone et al. .	
4,035,566	7/1977	Modest et al. .	
4,039,633	8/1977	Zelinski .	
4,039,663	8/1977	Penco et al. .	
4,039,736	8/1977	Bradner et al. .	
4,046,878	9/1977	Patelli et al.	514/34
4,058,519	11/1977	Arcamore et al.	514/34
4,067,969	1/1978	Penco et al. .	
4,075,328	2/1978	Ducep et al. .	
4,109,076	8/1978	Henry et al.	536/4
4,109,079	8/1978	Kawahara et al. .	
4,177,264	12/1979	Wu et al. .	
4,250,303	2/1981	Wu et al. .	
4,296,105	10/1981	Baurain et al. .	
4,325,947	4/1982	Penco et al. .	
4,327,087	4/1982	Rosenkrantz et al. .	
4,438,105	3/1984	Sarato et al. .	
4,537,593	8/1985	Alchas	604/411
4,564,054	1/1986	Gustavsson	141/329
4,576,211	3/1986	Valentini et al.	141/329
4,588,403	5/1986	Weiss et al.	604/411
4,675,311	6/1987	Gatti et al. .	
4,746,516	5/1988	Moro et al.	514/34
4,786,281	11/1988	Valentini et al.	604/256
4,946,831	8/1990	Gatti et al.	514/34

FOREIGN PATENT DOCUMENTS

1005760	2/1977	Canada .
1041488	10/1978	Canada .
1046507	1/1979	Canada .
1046508	1/1979	Canada .
1204738	5/1980	Canada .
1129344	8/1982	Canada .
1203482	4/1986	Canada .
129606	1/1985	European Pat. Off. .
0 401 896 A1	12/1990	European Pat. Off. .
2 314 725	1/1977	France .
2 432 525	2/1980	France .
29 27 452	1/1980	Germany .
35 36 896	4/1986	Germany .
60-92212	10/1983	Japan .
6092212	5/1985	Japan .
8502869	10/1985	Netherlands .
2 007 645	5/1979	United Kingdom .
2 124 224	2/1984	United Kingdom .
216751	4/1986	United Kingdom .
2 178 311	2/1987	United Kingdom .
985598	3/1995	United Kingdom .

OTHER PUBLICATIONS

Arcamone et al, "Structure and Physicochemical Properties", Internation Symposium on Adriamycin (1972) pp. 9–22.

Benvenuto et al, *American Journal of Hospital Pharmacy*, vol. 38 Dec. 1981, pp. 1914–1918.

Beijnen et al, *Pharmaceutical Weekblad Scientific Editor*, vol. 7 (1985) pp. 109–116.

Wasserman et al, *International Journal of Pharmaceuticals* vol. 19 (1983) pp. 73–78.

Bosanquet, *Cancer Chemother Pharmacol.* (1986) vol. 17 pp. 1–10.

Electrochemical Properties of Adriamycin Adsorbed on a Mercury Electrode Surface Bull. Chem. Soc. Japan, Sep., 1984; vol. 57, pp. 2383–2390; Kenji Kano, Tomonori Konse, Naomi Nishimura and Tanekazu Kubota.

The Effects of the pH and the Temmperature on the Oxidation–reduction Properties of Adriamycin Adsorbed on a Mercury Electrode Surface Bull. Chem. Soc. Japan, Feb. 1985; vol. 58, pp. 424–428; Kenji Kano, Tomonori Konse, and Tanekazu Kubota.

American Journal of Hospital Pharmacy, vol. 38, Dec. 1981, pp. 1914–1918, J. Benvenuto, et al., "Stability and Compatibility of Antitumor Agents in Glass and Plastic Containers".

Rote Liste, 1984, Preparation No. 85 031 (with English translation).

(List continued on next page.)

Primary Examiner—Elli Peselev

Attorney, Agent, or Firm—McDonnell, Boehnen, Hulbert & Berghoff

[57] **ABSTRACT**

According to the invention there is provided a sterile, pyrogen-free, ready-to-use solution of an anthracycline glycoside, especially doxorubicin, which consists essentially of a physiologically acceptable salt of an anthracycline glycoside dissolved in a physiologically acceptable solvent therefor, which has not been reconstituted from a lyophilizate and which has a pH of from 2.5 to 6.5. The solution of the invention is particularly advantageous for the administration by injection of the anthracycline glycoside drugs, e.g. doxorubicin, in the treatment of both human and animal tumors.

13 Claims, No Drawings

OTHER PUBLICATIONS

H. Bohme, et al., "Europaisches Arzneibuch III," 1979, p. 654 (with English translation).
The Interpharm International Dictionary of Biotechnology and Pharmaceutical Manufacturing, edited by Dean E. Synder, Publisher Buffalo Grove, IL: Interpharm Press, Inc., 1992.
Merck Index, 10th edition 1983, p. 499, entry 3,435.
Bosanquet, "Stability of solutions of antineoplastic agents during preparation and storage for in vitro assays", *Cancer Chemotherapy and Pharmacology,* vol. 17, 1986, pp. 1–10.
Rolf Kaltofen, Joachim Ziemann et al., *Tabellenbuch Chemie,* 12th edition, pp. 172, 181.
Yüksel, "Determination of Ceftriaxone in Aqueous Humour and Serum Samples by Differential–pulse Adsorptive Stripping Voltammetry", *Analyst,* vol. 119, 1994, pp. 1575–1577.
Falbe et al., *Rompp Chemie Lexikon,* 9th edition, Georg Thieme Verlag Stuttgart, New York, 1992, "Buffers", pp. 3677–3678.
Mortimer, *Chemie,* 3rd edition, Georg Thieme Verlag Stuttgart, New York, 1980, pp. 490–494.
Tan, C. et al., Daunomycin, an Anti–Tumor Antibiotic, in the Treatment of Neoplastic Disease, Mar. 1967, *Cancer* 20:333–353.
Samuels, L.D. et al., "Daunorubicin Therapy in Advanced Neuroblastoma", Apr. 1971, *Cancer* 27:831–834.
Miller, A.A. and Schmidt, C.G., "Clinical Pharmacology and Toxocology of 4Δ–O–tetrahydropyranyladriamycin", Mar. 1, 1987, *Cancer Research* 47:1461–1465.
Rozencweig, M. et al., "Preliminary Experience with Marcellomycin: Pre–Clinical and Clinical Aspects" p. 5499–561.
Arcamone et al. (1969), "Adriamycin, 14–Hydroxydaunomycin, a New Antitumor Antibiotic from *S. Peucetius* Var. *Caesius," Biotechnology and Bioengineering,* vol. XI, pp. 1101–1110.
Despois et al. (1967), "Isolement D'un Nouvel Antibiotique Doue D'Activite Antitumorale: La Rubidomycine (13.057 R.P.) Identite De La Rubidomycine et de La Daunomycine," *Path. Biol.,* vol. 15, pp. 887–891.
Lokich et al. (1983), "Constant Infusion Schedule for Adrimycin: A Phase I–II Clinical Trial of a 30–Day Schedule by Ambulatory Pump Delivery System," *J. Clinical Oncology,* vol. 1, pp. 24–28.
Wasserman and Bundgaard (1983), "Kinetics of the Acid–Catalyzed Hydrolysis of Doxorubicin," *International J. Pharmaceutics,* vol. 14, pp. 73–78.
Merck Index (1996), Mitoxantrone, 12th Edition, Entry 6303, p. 1064.
Martindale (1989), Mitotone, *The Pharmaceutical Press,* 29th Edition, London, Entry 1852–x, pp. 643–645.
ABPI Data Sheet Compendium, 1994–1995, "Novantron Injection," Lederle Laboratories, pp. 752–754.
Geigy Scientific Tables, vol. 3, *Physical Chemistry Composition of Blood Hematology Somatometric Data,* 8th revised and enlarged edition, Edited by C. Lentner, pp. 54–60.
Chemical Abstracts, vol. 92 (1980), 99512 c.
Chemical Abstracts, vol. 94 (1981), 214489f.
Chemical Abstracts, vol. 99 (1983), 146022z.
Chemical Abstracts, vol. 101 (1984), 122451x.
Chemical Abstracts, vol. 102 (1985), 209266k.
Chemical Abstracts, vol. 104 (1986), 39716d.
Arzneimittel–Forschung, vol. 17 (1967), pp. 934–939.
The Merck Index (1983) p. 3436.
Pharmaceutisch Weekblad, Scientific Edition, vol. 7, Jun. 21, 198 pp. 109–116.
Pharmaceutisch Weekbald, Scientific Edition, vol. 8, Apr. 25, 1986 pp. 109–133.
Journal of Chromatography 299 (1984), pp. 489–494.
Patent Abstracts of Japan (1956), 92212.
Martindale, The Extra Pharmacopoeia (1982), pp. 205–208.
Nor. Pharm. Acta, 45, 61–67 (1983).
J. Pharm. Biomed Anal., 2, 297–303 (1984).
American Journal of Hospital Pharmacy, vol. 38, pp. 483–486, Apr., 1981, G. K. Poochikian, et al., "Stability of Anthracycline Antitumor Agents in Four Infusion Fluids".
International Journal of Pharmaceutics, vol. 23, No. 1, pp. 1–11, Jan., 1985, M. J. H. Janssen, et al., "Doxorubicin Decomposition on Storage. Effect of pH, Type of Buffer and Liposome Encapsulation".
The United States Pharmacopeia, Twentieth revision, p. 266, Jul. 1, 1980.
Chemical Abstracts, vol. 88, p. 396, No. 197, p. 396, No. 197526X, 1978, T. Kaniewska, "Study of the Decomposition of Adriamycin".
Journal of Pharmaceutical Sciences, vol. 67, No. 6, pp. 782–785, Jun., 1978, S. Eksborg, "Extraction of Daunorubicin and Doxorubicin and Their Hydroxyl Metabolites: Self–Association in Aqueous Solution".
Journal of Pharmaceutical Sciences, vol. 73, No. 6, pp. 766–770, M. Memozzi, et al., "Self–Association of Doxorubicin and Related Compounds in Aqueous Solution".
International Symposium on Adriamycin, pp. 9–22, 1972, F. Arcamone, et al., "Structure and Physicochemical Properties of Adriamycin (Doxorubicin)".
Journal of Pharmaceutical and Biomedical Analysis, vol. 2, No. 2, pp. 297–303, 1984, S. Eksborg, et al., "Liquid Chromatography in Anticancer Drug Research with Special Reference to Anthraquinone Glycosides".
American Journal of Intravenous Therapy and Clinical Nutrition, vol. 8, No. 4, pp. 15–18, 1981, D. Ketchman, et al., "Cost Benefit and Stability Study of Doxorubicin Following Reconstitution".
Analytical Profiles of Drug Substances, vol. 9, pp. 245–274, 1980, A. Vigevani, et al., "Doxorubicin".
The Korean Pharmacopeia, 4 pages, 1977, Section "Injections".
The Guidelines for Examination for Each Industrial Field, Chapter "Medicament", 4 pages.
International Journal of Pharmaceutics, vol. 14, pp. 73–78, 1983, K. Wasserman, et al., Kinetics of the Acid–Catalyzed Hydrolysis of Doxorubicin.
American Journal of Hospital Pharmacy, vol. 36, pp. 1536–1538, 1979, D. M. Hoffman, et al., "Stability of Refrigerated and Frozen Solutions of Doxorubicin Hydrochloride".
Pharmaceutical Society of Japan Journal, vol. 104, No. 6, pp. 614–623, Jun., 1984, T. Masuike, et al., "Determination of Adriamycin and its Metabolities in Biological Samples Using High Performance Liquid Chromatography. I. Analysis of Serum and Plasma by Direct Injection Method. II. Analysis of Tissues by Extraction Method".
American Journal of Hospital Pharmacy, vol. 38, pp. 483–486, Apr., 1981, G. K. Poochikian, E et al., "Stability of Anthracycline Antitumor Agents in Four Infusion Fluids".
Dorr (1979), "Incompatibilities with Parenteral Anticancer Drugs," *The American Journal of Intravenous Therapy,* Feb./Mar., pp. 42, 45–46, 52.

Bernard, J., et al. (1969) *Rubidomycin,* Springer–Verlag, Berlin–Heidelberg–New York.

Karlsen, J., et al. (1983), "Stability of Cytotoxic Intravenous Solutions Subjected to Freeze–Thaw Treatment", *Nor. Pharm Acta,* vol. 45, pp. 61–67.

Vogelzang, N.J., et al. (1985), "Phase I Trial of an Implanted Battery–Powered, Programmable Drug Delivery System for Continuous Doxorubicin Administration," *Journal of Clinical Oncology,* vol. 3, No. 3 (Mar.), pp. 407–414.

Falk, K., et al. (1979), "Mutagenicity in Urine of Nurses Handling Cytostatic Drugs", *The Lancet,* Jun. 9, 1979, pp. 1250–1251.

"Union Warns of Cancer Drug Dangers", *Chemistry and Industry,* Jul. 4, 1983.

Lassila, O., et al. (1980), "Immune Function in Nurses Handling cytostatic Drugs", *The Lancet,* Aug. 30, 1980., p. 482.

Abstract of Medical Economics Co., *Chemistry–Industry,* Feb. 7, 1983, p. 99.

Chemical Abstract, vol. 99, p. 345 (1983), Abst. No. 99:218014y.

Topics in Antibiotic Chemistry, 2, 109–115, 1978.

Young et al.. The Anthracycline Antineoplastic Drugs (1981) vol. 305(3) New England J. Med 139.

Casazza, Experimental Studies on New Anthracyclines (1984) (Proc. of Int. Symposium on Adriamycin: Ogawa et al. eds.).

Aubel Sadron et al., Daunorubicin and doxorubicin, anthracycline antibiotics, a physicochemical and biological review (1984) Biochemie 66, pp. 333–352.

Abdella et al., A Chemical perspective on the Anthracycline Antitumor Antibiotics, Env. Health Persp. vol. 64, pp. 3–18 (1985).

Arcamone, Daunomycin and Related Antibiotics. Topics in Antibiotic Chemistry. vol. 2 (Sammes, ed.) (1978).

Brown, Adriamycin and Related Anthracycline Antibiotics, Prog. Med. Chem. 15:124 (1978).

Goormagtigh et al., Anthracycline Glycoside–Membrane Interactions, Biochem. Biophys. Acta: 271–288 (1984).

Skovsgaard et al., Adrimycin, An Antitumor Antibiotic : A Review with Special Reference to Daunomycin, Dan. Med. Bull 22(2):62 (1975).

Bachur et al., Cellular pharmacodynamics of several anthracycline antibiotics (1976) J. Med. Chem 19(5):651.

Suarato, "Antitumor Anthracyclines", *The Chemistry of Antiumour Agents* (1990) (Wilman, ed.).

Legha; "The Anthracyclines and Mitoxantrone", *Cancer Chemotheraphy by Infusion* 2nd edition (Lokich et.) (1990) Precept Press.

Bouma et al., Anthracycline Antitumor agents: A review of physcicochemical, analytical and stability properties Pharm. Weekblad Sc. Ed., vol. 8, p. 109 (1986).

Williams, Stabillity & Compatibility of Admixtures of Antineoplastic Drugs, *Cancer Chemotherapyhy by Infusion.* 2nd Edition (Lukich et.) (1990) Precept Press.

Williams et al., Photoinactivation of Anthracyclines (1981) Photochemistry & Photobiology, vol. 34, p. 131.

Poochikian et al., Stability of anthracycline antitumor agents in four infusion fluids (1981) Chemical Abstracts, vol. 94.214489f.

Keusters, et al., Stability of solutions of doxorubicin and epirubicin in plastic mini bags for intravesical use after storage at –20° C. and thawing by microwave radiation. (1986) Pharm. Weekblad Sc.Ed. vol. 8 p. 144.

Bekers et al., Effect of cyclodextrins on anthracycline stability in acidic aqueous media (1988) Pharm. Weekblad. S. Ed., vol. 10.,207.

Wood, Mary Jayne: Stability of anthracycline cytotoxic agents in solution and infusion fluids–submitted for the degree of Master of Philosophy (The University of Aston in Birmingham). Oct. 1988.

Wood et al., Stability of Doxorubicin, Daunorubicin and Epirubxcin in Plastic Syringes and Minibags (1990) J. Clin. Pharm. Therapeutics vol. 15. p. 279–289.

Crom et al., Pharmacokinetics of Anticancer Drugs in Children, Clin. Pharm. 12:pp. 168–213 (1987).

Greidanus, et al., "Continuous Infusion of Low–dose Doxorubicin, Epirubicin and Mitoxantrone", *Cancer Chemotherapy: A Review,* (1988) Pharm. Weekblad. Sci. Ed., vol. 10, p. 237.

Bachur et al., Daunorubicin and adriamycin metabolism in the golden syrian hamster (1973) Biochem. Med. vol. 8, p. 352.

Haneke et al., Quanititation of Daunorubicin, Doxorubicin, and their Aglycones by Ion–Pair Reversed–Phase Chromarography, J. Pharm. Sci. 70(10): 1112 (1981).

Tomlinson et al., Concomitant Adsorption and Stability of Sonic Anthracycline Antibiotics (Oct. 1982) 71 (10) J. Pharm Sci. 1121.

Von Hoff et al., Daunomycin: An Anthracycline Antibiotic Effective in Acute Leukemia, Adv. Pharm. Chemo. 15:1 (1978).

Cassinelli et al., La Daunomicina: Un Nuovo Antibiotico Ad Attivita Citostatica Isolamento E Proprieta (1963) Giorn. Microbial. 11:167.

Arcamone, La Constitution Chimique de la Daunomycine, Path. Biol. 15(19–20): 893 (1967).

Di Marco et al., Daunomycin, a New Antibiotic of the Rhodomycin Group, Nature 201: 706 (1964).

Angiuli et al., Structure of Daunomycin, X–Ray Analysis of N–Br–Acetyl–Daunomycin Solvate, Nature New Biol., 234:78 (Nov. 1971).

Trissel et al.; Investigational Drug Information (1978) Drug Intell. Clin. Pharm vol. 12, p. 404.

Handbook on Injectable Drugs (Trissel) 2nd Ed. 1980, p. 562.

Handbook on Injectable Drugs (Trissel) 5th Edition (1988), p. 222–223.

AHFS Drug Information 1984, p. 249–250.

AHFS Drug Information 1990, p. 501–503.

Fischer et al., The Cancer Chemotherapy Handbook 3rd Edition (1989), p. 65–69.

Drug Information for the Health Care Professional USP DI 1991—11th Edition, p. 1080–1084.

Beijnen, et al., Structure Elucidation and Characterization of Daunorubicin Degradation Products (1987) Int. J. Pharm., vol. 34, p. 247.

Bachur, Daunomycin Metabolism in Rat Tissue Slices., J. Pharm. Exp. Ther. 175(2):331.

Riley, et al., Review of New Drugs—1980, U.S. Pharm. 33 (Feb.1981).

Boiron et al., Daunorubicin in the Treatment of Acute Myelocytic Leukemia. The Lancet. (Feb. 1969), p. 330.

Di Marco et al., Activity of Adriamycin (NSC 123127) and Daunomycin (NSC 82151) Against Mouse Mammary Carcinoma, Cancer Chemother. Rep., part 1, vol. 56(2):153 (1972).

Barthelemy–Clavey et al., Self–Association of Daunorubicin, FEBS Lett., vol. 46(1), p. 5 (1974).

Calendi et al., On Physico–Chemical Interactions between Daunomycin and Nucleic Acids, Biochem Biophys. Acta., vol. 103:25. (1965).

Schreier, Binding of Daunomycin to Acidic Phospholipids J. Par. Sci. Tech, vol. 43, No. 4, p. 213 (1989).

Dubost et al., Un nouvel antibiotique a proprieties cytostatiques: la rubidomycine (1963) C.R. Acad. Sci. Paris, 257, p. 813.

Maral et al., Etude Toxicologique et activite Antitumorale Experimentale de la Rubidomycine (13.057 R.P.) Path. Biol., vol. 15, No. 19–20, pp. 903–908 (1967).

Depois et al: Un nouvel antibiotique dove d'activite antitumorale la rubidomycine (13.057 R.P.), J. Preparation et properties, Arzicial Forsch. 17:934 (1967).

Brazhnikova et al., Physicochemical Properties of Antitumour Antibiotic Rubomycin produced by Act. Cocruleorubidus (1986) Antibiotki 11:763.

"Discovery & Development of Doxorubicin", *Doxorubicin, Anticancer Antibiotics* (Arcamone, eds.) (1981) Academic Press, pp. 1–47.

Blum et al., Adriamycin: A New Anticancer Drug with Significant Clinical Activity, Annals of Int. Med., 80:249–259 (1974).

Arcamone et al., Adriamycin (14–Hydroxydaunomycin), a Novel Antitumor Antibiotic Tetrahedron Letters No. 13, p. 1007–1010.

Di Marco et al., Adriamycin, a New Antibiotic, Antitumour, Activity, Cancer Chem. Reports, part 1, vol. 53, No. 1, p. 33 (1969).

Trissel: A Handbook on Injectable Drugs 2nd edition (1980), p. 196.

Trissel: A Handbook on Injectable Drugs 4th edition (1986), p. 215–217.

Trissel: A Handbook on Injectable Drugs 5th edition (1988), p. 259–264.

McEvoy, AHFS Drug Information 1984, p. 251–254.

AHFS Drug Information 1990, p. 504–507.

Fischer, The Cancer Chemotherapy Handbook 3rd edition (1989), p. 82–87.

Drug Information for the Health Care Professional USP DI (1991) 11th Edition, p. 1217–1222.

Benvenuto et al., Stability & Compatibility of Antitumor Agents in Glass & Plastic Containers, (Dec. 1981), Am. J. Hosp. Pharm., vol. 38, p. 1914.

Walker et al., Doxorubicin Stability in Syringes and Glass Vials and Evaluation of Chemical Contamination, Can J. Hosp. Pharm. 44(2): 71(1991).

Gupta et al., Investigation of the Stability of Doxorubicin Hydrochloride using Factorial Design, Drug Development & Industrial Pharmacy, (1988) vol. 14(12) p. 1657–1671.

Beijnen et al., Stability of intravenous admixtures of doxorubicin and vincristine. Am. J. Hosp. Pharm., vol. 43, p. 3022, (Dec. 1986).

Asker et al., Effect of Glutathione on Photolytic Degradation of Doxorubicin Hydrochloride, J. Par. Sci. Tech. (1988), 42(5)193.

Habib et al., Photostabilization of doxorubicin Hydrochloride with Radioprotective and Photoprotective Agents: Potential Mechanism for Enhancing Chemotherapy during Radiotherapy (Nov.–Dec. 1989) 43 J. Parenteral Science & Technology, vol. 43, No. 6, p. 254, (Nov.–Dec,. 1989).

Speth, et al., Clinical Pharmacokinetics of Doxorubicin, Clin. Pharm., vol. 15, pp. 15–31, (1988).

Yee et al., Adriamycin: A Brief Review (Apr., 1981) Am. J. Int. Ther. Clin Nut. pp. 7–12.

Hoffman et al., Stability of Refrigerated and Frozen Solutions of Doxorubicin Hydrochloride (Nov. 1979), Am. J. Hosp. Pharm. vol. 36(11) 1536–1538.

Karlsen et al., Stability of cytotoxic intravenous solutions subjected to freeze–thaw treatment (1983), Chemical Abstracts, vol. 99, No. 146022, p. 374.

Gaj., et al., Compatibility of Doxorubicin Hydrochloride and Vinblastine Sulfate—The Stability of a Solution Stored in Cormed ®Reservoir Bags or Monoject® Plastic Syringes (May, 1984) Am. J. IV Ther. Clin. Nut., p. 8.

Tavoloni et al., Photolytic Degradation of Adriamycin (1980) Comm. J. Pharm. Pharmacol. vol., 32, p. 860.

Garnick et al., Phase 1 Trial of Long Term Continuous Adriamycin Administration, Proc. Am. Soc. Clin. Oncol., C–106: p. 359, (Mar. 1981).

Lokich et al., Constant Infusion Schedule for Adriamycin: A Phase I–II Clinical Trial of a 30–Day Schedule by Ambulatory Pump Delivery System, J. Clin. Oncol., vol. 1 (1): 24 (1983).

Vogelzang et al., Continuous Doxorubicin Infusion (CDI) Using an Implanted Lithium Battery–Powered Drug Administration Device System, Proc. Am.Soc. Clin.Uncol. C–1030: p. 263, (Mar. 1984).

Legha et al., Reduction of Doxorubicin Cardiotoxicity by Prolonged Continuous Intravenous Infusion, Ann. Int. Med., vol. 96, No. 2, p. 133 (1982).

Pavlik et al., Stability of Doxorubicin in Relation to Chemosensitivity Determinations: Loss of Lethality and Retention of Antiproliferative Activity (1984), Cancer Investigation 2 (6), 449–458.

Dozier et al., Practical Considerations in the Preparation and Administration of Cancer Chemotherapy (Sep. 1983) Am.J. Int. Ther. Clin. Nut., p. 6.

Kirschenbaum et al: Stability of injectable medications after reconstitution, Am. J. Hosp. Pharm.: 33:767–790 (Aug., 1976).

Janssen et al., Doxorubicin decomposition on storage. Effect of pH., type of buffer and liposome encapsulation, (1985) Chemical Abstracts, vol. 102, No. 209226k.

Crommelin et al., Preparation and characterization of doxorubicin–containing liposomes. II. Loading capacity, long–term stability and of doxorubicin–bilayer interaction mechanism (1983) Int. J. Pharm. vol. 17, p. 135.

Van Bommel, et al., Stability of Doxorubicin–Liposomes on Storage: as an Aqueous Dispersion, Frozen or Freeze dried (1984), Int. J. Pharm., vol. 22, pp. 299–310.

Crommelin et al., Preparation and characterization of doxorubicin–containing lipsomes: I. Influence of liposome charge and pH of hydration medium on loading capacity and particle size, (1983), Int. J. Pharm., vol. 16, pp. 93–96.

Gupta et al., "Influence of Stabilization Temperature on the Entrapment of Adriamycin", *Albumin Microspheres Drug. Dev. Int. Pharm.*, vol. 13, No. 8, pp. 1471–1482, (1987).

Yanagawa et al., Stability and Releasibility of Adriamycin Ointment (1983).

Vilallonga et al: Interaction of Doxorubicin with Phospholipid Monolayers, J. Pharm. Sci. 67(6), p. 773 (1978).

Duarte–Karim et al., Affinity of adriamycin to phospholipids. A possible explanation for cardiac mirochonorial lesions., (1976) Biochem Biophy. Research Comm., 71(2), p. 658.

Bonadonna et al., Clinical Evaluation of Adriamycin a New Antitumor Antibiotic, Br. Med. J., (3), 503 (Aug. 1969).

Banks et al., Topical Installation of Doxorubicin Hydrochloride in the Treatment of Recurring Superficial Transitional Cell Carinoma of the Bladder, J. Ulrol., vol. 118, p. 757 (1977).

Bertazzoli et al., Chronic toxicity of adriamycin: a new antineoplastic antibiotic (1972), Tox. Applied Pharm., vol. 2, pp. 287–301.

Wang et al., Therapeutic effect and toxicity of adriamycin in patients with neoplastic disease, (1971) Cancer, 28, p. 837.

Horn et al., Intravesical chemotherapy in a controlled trial with thio–tepa versus doxorubicin hydrochloride (1981) J. Urol., 125:652.

Jacobi et al., Studies on the intravesical action of topically administered G3H–doxorubicin hydrochloride in men: plasma uptake and tumor penetration (1980), J. Urol. 124:34.

Jaenke, R.S.: Delayed and progressive myocardial lesions after adriamycin administration in the rabbit. (1976) Cancer Res. vol. 36, pp. 2958–2966.

Casazza et al., Tumors and dental ocular abnormalities after treatment of infant rats with adriamycin, (1977) Tumor 63:331.

Barranco et al., Survival and cell kinetics effects of adriamycin on mammalian cells, (1973). Cancer Res. 33:11.

Gaj et al., Evaluation of growth in Five Microorganisms in Doxorubicin and Floxuridine Media, (1984) Pharm. Manuf., p. 50.

Sturgeon and Schulman: Electronic Absorption Spectra and Protolytic Equlibria of Doxorubicin: Direct Spectrophotometric Determination of Microconstants, J. Pharm. Sci. 66(7):958, (1977).

Dalmark et al., A Fickian Diffusion Transport Process with Features of Transport Catalysis, J. Gen Physiol. 78:349 (1981).

Masuike et al., Determination of Adriamycin and its Metabolities in Biological samples using high performance liquid chromatography Chemical Abstracts (1984), vol. 101, p. 5.

Barth et al., "Determination of Doxorubicin Hydrochloride.", Pharamaceutical Preparations using High Pressure Liquid Chromatography, (1977) J. of Chromatography vol. 131, p. 375–381.

Arena et al., Analysis of the pharmacokinetic characteristics, pharmacological and chemotherapeutic activity of 14–hydroxy–daunomycin (adriamycin), a new drug endowed with an Antitumor activity, (1971) Drug Res. 21: 1258.

Watson et al., Rapid analytic method for adriamycin and metabolites in human plasma by a thin fim flourescence scanner (1976) Cancer Treat. Rep., vol. 60, No. 11, p. 1611.

Langone et al., Adriamycin and Metabolites: Separation by High Pressure Liquid Chromatography and Qunitation by Radioimmunossay, Biochem Med. 12:283 (1975).

Benjamin et al., Pharmacokinetics and metabolism of adriamycin in man, Clin. Pharm. Ther., 14(4) Part 1, 592.

Epirubicin, Drugs of the Future, vol. 8,(5): p. 402, (1985).

Cersosimo et al., Epirubicin: A Review of the Pharmacology, Clinical Activity , and Adverse Effects of an Adriamycin Analogue, J. Clin. Oncol 4(3), 425 (1986).

Fischer, "The Cancer Chemotherapy Handbook", 3rd Edition, (1989), p. 87–89.

DeVroe, et. al., A Study on the stability of three antineoplastic drugs and on their sorption by i.v. delivery systems and end–line filters, (1990), Int. J. Pharm. vol. 65, p. 49–56.

DeVries, et. al., A Phase 1 and Pharmocokinetic Study with 21 day Continuous infusion of Epirubicin., J. Clin. Oncol., (1987), 5(9), 1445–1451.

Adams, et. al, Pharmaceutical Apsects of Home Infusion Therapy for Cancer Patients, (Apr. 1987), Pharm J., p. 476.

Weenen, et. al., "Pharmacokinetics of 4–Epi–doxorubicin in Man", Invesi. New Drugs, vol. 1, (1983), p. 59.

Arcamone, et. al., "Synthesis and Antitumour Activity of 4–Demethoxydaunorubicin, 4–Demothoxy–7,9–diepidaunorubicin, and their beta anomers", Cancer Treat Rep. 60(7):829 (1976).

Turowski et al., "Visual Compatability of Idarubicin Hydrochloride with selected drugs during simulated Y–site injection", (Oct. 1991), Ans. J. Hosp. Pharm., vol. 48, p. 2181.

Hurteloup et al., Phase II Trial of Idarubicin (4–Demethoxydaunorubicin) in Advanced Breast Cancer, Eur. J. Cancer Clin. Oncol. 25(3)423 (1989).

Kaplan et al., Phase I Trial of 4– Demethoxydaunorubicin with single i.v. doses, Eur. J. Clin. Cancer Oncol., 18(12) 1303 (1982).

Reich et al., "Carminomycin, *Arptheacyclines: Current Status and New Developments,"*(1980) (J. Cooke et al., eds.) Academic Press, p. 295.

Brazhnikova et al., "Physical and Chemical Characteristics and Structure of Carminomycin, a New Antitumour Antibiotic", J. Antibiot, 27(4):254 (1974).

Brazhnikova et al., "Carminomycin, a New Antitumour Anthracycline" (1973) Antibiotiki 18:681.

Crooke, "A Review of Carminomycin, A New Anthracycline Developed in the USSR" J. Med. 8(5):295 (1977).

Lankelma et al, "Plasma Concentrations of Carminomycin and Carminomycinol in Man, Measured in High Pressure Liquid Chromatography", Eur. J. Cancer clin. Oncol. 18(4):363 (1982).

Fandrich, "Analysis of Carminomycin in Human Serum by Fluorometric High–Performance Liquid Chromatography", J. Chromatogr. 223 115 (1981).

Oki, "Aclacinomycin A Anthracyclines: Current Status and New Developments", (1980) Academic Press., p. 323.

Oki et al., "Antitumour Anthracycline Antibiotics, Aclacinomycin A and Analogues: I. Taxonomy, Production, Isolation and Physicochemical Properties", J. Antibiot 32(8):791 (1979).

Oki, "New Antitumour Antibiotics, Aclacinomycins A and B", J. Antibiot, 28(10):830 (1975).

Mori et al., "Physicochemical Properties and Stability of Aclacinomycin A Hydrochloride," (1980), Jpn. J. Antibiot 33:618.

Trissel, "Handbook on Injectable Drugs", 5th Edition, p. 707.

Fischer, "The Cancer Chemotherapy Handbook", 3rd Edition, pp. 17–19.

Arcamone et al., "Synthesis and Antitumour Activity of 4–Deoxydaunorubicin and 4–Deoxyadriamycin", J. Med. Chem. 19(12):1424 (1976).

Fischer, "The Cancer Chemotherapy Handbook" 3rd Edition (1989), p. 88.

Salmon et al., "Antitumour Activity of Esorubicin in Human Tumour Clonogenic Assay with Comparison to Doxorubicin", J. Clin. Oncol. 2(4):282 (1984).

Kovach et al., "Phase I Trial & Assay of Rubidozone (NSC 164011) in Patients with Advanced Solid Tumors", (Mar. 1979) Cancer Research vol. 39, p. 823.

Deprez–de Campanere et al., "Pharmacokinetic, Toxicologic, and Chemotherapeutic Properties of Detorubicin in Mice: A Comparative Study with Daunourubicin and Adriamycin", Cancer Treat. Rep., 63(5):861 (1979).

Bono, "The Preclinical Development of Quelamycin and its Initial Clinical Trials.", *Aruthracyclines: Current Status and New Developments,* (1980) Academic Press, p 315.

Gosalvez et al., "Quelamycin, a New Derivative of Adriamycin with Several Possible Therapeutic Advantages", Eur. J. Cancer 14:1185 (1978).

Reich et al., "Marcellomycin *Anthracyclines: Current Status and New Developments",* (1980) Academic Press, p. 343.

Nettleston et al., New Antitumour Antibiotics: Musettamycin and Marcellomycin from Bohemic Acid Complex: (1977) 30(6) J. Antibiotics 525.

Israel et al., "Adriamycin Analogues: Preparation and Biological Evaulation of Some N–Perfluoroacyl Analogues of Daunorubicin, Adriamycin, and N–(trifluoroacetyl) adriamycin 14–valerate and their 9,10–Anhydro Derivatives" J. Med. Chem. 25:187 (1982).

Tong et al., "5–Iminodaunorubicin: Reduced Cardiotoxic Properties in an Antitumour Anthracycline", J. Med. Chem. 22(1): 36 (1979).

Arcamone et al., "Synthesis and Antitumour Activity of new Daunorubicin and Adriamycin Analogues" (1978) Experientia 34:1255.

Umezawa et al., "Tetrahydropyranyl Derivatives of Daunomycin and Adriamycin", J. Antibiot 32(10):1082 (1979).

Chen et al., "Possible Strategies for the Formulation of Antineoplastic Drugs" (1986) Drug. Dev. Ind. Pharm. vol. 12(7) 1041.

Pharmaceutics—The science of dosage form design (Aulton) (1988), pp. 242–244, 252–253, 368–369, 374–375, 380–.

Experimental Pharmaceutical Technology, 2nd Ed.(Parrott & Saski), 1965, pp. 132–134, 149–154.

Pharmaceutics & Pharmacy Practice (1982) (Banker & Chalmers), pp. 238–243, 275–278.

Pharmaceutical Dosage Forms: Parenteral Medications: vol. 1 (Avis et al. 1984) "Biopharmaceutics of Injectable Medication" (Motola).

Connors et al., "Chemical Stability of Pharmaceuticals—a Handbook for Pharmacists" (1979) Wiley, pp. 3–7, 44–63, 74–75.

Ozturk et al., "Dissolution of Ionizable Drugs in Buffered and Unbuffered Solutions" (1988) 5(5) Pharm. Res. 272.

Gordon et al., "The Art and Science of Contemporary Drug Development", Prog. Drug. Res. 16:194 (1972).

Pharmaceutical Dosage Forms: Parenteral Medications: vol. 1 (Avis et al., 1984), "Preformulation Research of Parenteral Medications" (Motola & Agharkar).

The Theory & Practice of Industrial Pharmacy (Lachman et al.), 3rd Ed. 1986, p. 191, et seq., pp. 191–194, 195–196, 459–460, 471–472, 477–478, 764–765.

Lin, "Kinetic Study in Formulation Investigation of New Compounds" (1968).

Zoglio, "Preformulation Stability Testing of Parenteral Products" (1968).

Knoop, "The Pharmaceutical Drug Development Process: An Overview" (1988) 22 Drug. Inf. J. 259.

Rees, "Physico–Mechanical Pre–Formulation Studies" (1973) 112 Boll. Chim. Farm. 216.

Monkhouse, "Dosage Forms For Clinical Trials" (1985) 11 (9 & 10) Drug. Dev. Ind. Pharm. 1729.

Graffner et al., "Preformulation Studies in a Drug Development Program for Tablet Formulations", J. Pharm. Sci. 74(1) 16 (1985).

Davignon et al., Pharmaceutical Aspects of Antitumour Agents (1984) Pharm. Weekbt. 119:1144.

Pharmaceutical Dosage Forms: Parenteral Medications: vol. 2 (Avis et al., 1984) "Formulation for Large Volume Parenterals" (Demorest), pp. 55–63, 68–70, 73–76, 83.

Pharmaceutical Dosage Forms: Parenteral Medications: vol. 1(Avis et al., 1984) "Formulation for Small Volume Parenterals" (DeLuca & Boylan).

Schumacher (ed), Bulk Compounding Technology.

Carlin, "Incompatibilities of Parenteral Medications" (Jun. 1968) 25 Am. J. Hosp. Pharm. 271.

Kalmas, et al., "Solubility Aspects in Parenteral Formulation" (May/Jun. 1982) Ind. J. Hosp. Pharm. 94, pp. 94–96, 98, Table I.

Parrott, Formulation of Parenterals.

Lin, "Parenteral Formulations I. Comparisons of Accelarated Stability Data with Shelf–Life Studies", Bull. Par. Drug Assoc. 23(6):269.

Lin, "Parenteral Formulations II. A Stability Testing Program for Parenteral Products", Bull. Par. Drug. Assoc. 24(2):83.

Lin, "Photochemical Considerations of Parenteral Products", Bull. Par. Drug. Assoc. 23 (4):149.

National Coordinating Committee on Large Volume Parenterals, "Recommendations to Pharmacists for Solving Problems with Large–Volume Parenterals", Am. J. Hosp. Pharm. 33:231 (1976).

Zellmer, "Solving Problems with Large–Volume Parenterals, 1: Pharmacist Responsibility for Compounding Intravenous Admixtures", Am. J. Hosp. Pharm. 32:255 (1975).

Pharmaceutical Dosage Forms, "Parenteral Medications: vol. 1 (Avis et al. 1984)—Parenteral Drug Administration: Routes, Precautions, Problems & Complications" (Duma & Akers).

Edward, "pH: An important Factor in the Compatibility of Additives In Intravenous Therapy" (Aug. 1967) vol. 24 Am. J. Hosp. Pharm. 440.

Document entitled "Kinetic pH Profiles", pp. 59–121, 380–385.

Remington's Pharmaceutical Sciences, 18th ed. 1990; ch. 17: Ionic Solutions & Electrolytic Equilibria.

Advances in Pharmaceutical Services, vol. 2 (Bean et al., 1967), pp. 62–75, 80–95.

Fynn, "Buffers–pH Control within Pharmaceutical Systems" (Mar.–Apr. 1980) vol. 34 (2) J. Parenteral Drug Assoc. 139.

Windheuser, "The Effect of Buffers on Parenteral Solutions" (Sep./Oct. 1963) vol. 17(5) Bull Parenteral Drug Assoc.

Rubino, "The Effects of Cosolvents on the Action of Pharmaceutical Buffers" (1987) 41(2) J. Paren. Sci. Tech. 45.

Kramer & Flynn, "Solubility of Organic Hydrochlorides" (Dec. 1972) vol. 61 (12) J. Pharm. Sci. 1896.

Tencheva et al., "New Approach of the Extrapolation Procedure in the Determination of Acid–Base Constants of Poorly Soluble Pharmaceuticals" (1979); Arzneim Forsch/ Drug Res. 29 (II) #9.

Bogardus et al., "Solubility of Doxycycline in Aqueous Solutions" (Feb. 1979) vol. 68 (2) J. Pharm. Sci. 188.

Miyazaki et al., "Precaution on Use of Hydrochloride Salts in Pharmaceutical Formulation" (Jun. 1981) 70(6) J. Pharm. Sci. 594.

Greene et al.: Stability of cicplatin in aqueous solution, Am J. Hosp. Pharm. 36:38 (1979).

Stjernstrom et al: Studies on the stability and compatibility of drugs in infusion fluids, Acta Pharm Spec. 15:33 (1978).
Ho: Prediction of Pharmaceutical Stability of Parenteral Solutions III (Feb. 1971) vol. 5, Drug, Int. Clin. Pharm. 47.
Stella: Chemical and Physical Bases Determining the Instability and Incompatibility of Formulated Injectable Drugs (1986) 40(4) J. Paren. Sci. Tech. 142.
Newton: "Physicochemical Determinants of Incompatibility and Instability in Injectable Drug Solutions and Admixtures" (1978 35 Am. J. Hosp. Pharm. 1213.
Mendenhall: Stability of Parenterals (1984) Drugs Dev. Ind. Pharm. 10(8–9) 1297.
Singh et al.: Effect of Solvents and Additives on the Stability of Drugs, Pharma Times 13.
Pope: Accelerated Stability Testing for Prediction of Drug Product Stability—First of a Two–Part Article (Nov., 1980) D & CI 54, pp. 54, 56, 59, 60, 62, 116.
Pope: Accelerated Stability Testing for Prediction of Drug Product Stability—Second of a Two–Part Article (Dec., 1980) D & CI 48, pp. 48, 50, 55, 56, 58, 60, 62, 64–66, 110, 112–116.
Amirjahed: Simplified Method to Study Stability of Pharmaceutical Preparations, J. Pharm. Sci. p. (6):785 (1977).
Vogenberg et al.: Stability Guidelines for Routinely Refrigerated Drug Products, Am. J. Hosp. Pharm. 40:101(1983).
Newton et al.: Estimating shelf–life of drugs in solution. Am. J. Hosp. Pharm. 44:1633 (1987).
Mollica et al.: Stability of Pharmaceuticals. J. Pharm. Sci. 67(4):443 (1978).
King et al: Statistical Prediction of Drug Stability Based on Non–Linear Parameter Extension, J. Pharm. Sci. 73(5):657.
Herrick et al.; Monetary incentive for pharmacists to control drug costs; (Jul. 1985) vol. 42, Am. J. Hosp. Pharm. 1527.
Waller: Documenting i.v. admixture product waste (Aug. 1980) vol. 43, Am. J. Hosp. Pharm. 1914.
Williams et al.: The Lyophilization of Pharmaceuticals: A Literature Review (1984) 38(2) J.. Paren. Sci. Tech. 48.
Flamberg et al.: Manufacturing Considerations in the Lyophilization of Parenteral Products (1986) Pharm. Manuf.3:29–31.
Maral et al.: Un Nouvel Antibiotique Doue D'Activite Antitumorale: La Rubidomycine (13 057 R.P.), II: Activite antitumorale experimentale Arzncimittel Forsch (1967) 17:939.
Beijnen et al.: Aspects of the Degradation Kinetics of Doxorubicin in Aqueous Solution (1986) 32 Int. J. Pharm. 123.
Gjelstrup et al., Almen Farmaci II (1983).
Handbook on Injectible Drugs 3rd Ed. (Trissel), 1983.
Wang et al., "Review of Excipients and pH's for Parenteral Products Used in the United States", Journal of the Parenteral Drug Association 14(6):452 (1980).
Jonkman–de Vries et al., "Pharmaceutical Development of a Parental Lyophilized Formulation of the Novel Indoloquinone Antitumor Agent EO", Cancer Chemother. Pharmacol. 34:416–422 (1994).
Pharmaceutical Sciences, Mack Publishing, (1980), p. 1365–1366.
The Pharmaceutical Codex 11th Ed., 1979, p. 446–447.
The Pharmaceutical Codex 12th Ed. (Lund), 1994, p. 201.
Kjeld Ilver: Almen Galenisk Farmaci—Forel sningsnoter, Dansk Farmaceutforenings Forlag 1971.
Sv. Aage Schou & V. Gaun Jensen: Tr k af den glaeniske farmaci, Store Nordiske Videnskabsboghandel, 1959.
Almen Farmaci, Dansk Farmaceutforenings Forlag 1980.
Erik Sandell: Galenisk Farmaci, 2nd edition, Stockholm 1967.
Erik Sandell: Galenisk Farmaci, 3rd edition, Stockholm 1982.
Alfred N. Martin et al., Physikalische Pharmazie 1975, p. 239.
European Pharmacopeia, vol. III, 1979, p. 656: Citations—D 14.

INJECTABLE READY-TO-USE SOLUTIONS CONTAINING AN ANTITUMOR ANTHRACYCLINE GLYCOSIDE

This is a division of application Ser. No. 07/503,856, filed on Apr. 3, 1990, now U.S. Pat. No. 5,124,317.

The present invention relates to a stable intravenously injectable ready-to-use solution of an antitumor anthracycline glycoside, e.g. doxorubicin, to a process for preparing such a solution, and provide the same in a sealed container, and to a method for treating tumors by the use of the said ready-to-use solution.

The anthracycline glycoside compounds are a well known class of compounds in the antineoplastic group of agents, wherein doxorubicin is a typical, and the most widely used, representative: Doxorubicin. Anticancer Antibiotics, Federico Arcamone, 1981, Publ: Academic Press, New York, N.Y.; Adriamycin Review, EROTC International Symposium, Brussels, May, 1974, edited by M.Staquet, Publ. Eur. Press Medikon, Ghent, Belg.;

Results of Adriamycin Therapy, Adriamycin Symposium at Frankfurt/Main 1974 edited by M. Ghione, J. Fetzer and H. Maier, publ.: Springer, New York, N.Y.

At present, anthracycline glycoside antitumor drugs, in particular, e.g., doxorubicin, are solely available in the form of lyophilized preparations, which need to be Reconstituted before administration.

Both the manufacturing and the reconstitution of such preparations expose the involved personnel (workers, pharmacists, medical personnel, nurses) to risks of contamination which are particularly serious due to the toxicity of the antitumor substances.

The Martindale Extra Pharmacopoeia 28th edition, page 175 left column, reports, indeed, about adverse effects of antineoplastic drugs and recommends that "They must be handled with great care and contact with skin and eyes avoided; they should not be inhaled. Care must be taken to avoid extravasation since pain and tissue damage may ensue."

Similarly, Scand. J. Work Environ Health vol.10 (2), pages 71–74 (1984), as well as articles on Chemistry Industry, Issue Jul. 4, 1983, page 488, and Drug-Topics-Medical-Economics-Co, Issue Feb. 7, 1983, page 99 report about severe adverse effects observed in medical personnel exposed to use of cytostatic agents, including doxorubicin.

To administer a lyophilized preparation, double handling of the drug is required, the lyophilized cake having to be first reconstituted and then administered and,moreover,in some cases, the complete dissolution of the powder may require prolonged shaking because of solubilization problems.

As the risks connected with the manufacturing and the reconstitution of a lyophilized preparate would be highly reduced if a ready-to-use solution of the drug were available, we have developed a stable, therapeutically acceptable intravenously injectable solution of an anthracycline glycoside drug, e.g. doxorubicin, whose preparation and administration does not require either lyophilization or reconstitution.

According to the present invention, there is provided a sterile, pyrogen-free, anthracycline glycoside solution which consists essentially of a physiologically acceptable salt of an anthracycline glycoside dissolved in a physiologically acceptable solvent therefor, which has not been reconstituted from a lyophilizate and which has a pH of from 2.5 to 6.5.

Preferably the solution of the invention is provided in a sealed container.

Preferably the anthracycline glycoside is chosen from the group consisting of doxorubicin, 4'-epi-doxorubicin (i.e. epirubicin), 4'-desoxy-doxorubicin (i.e. esorubicin), 4'-desoxy-4'-iodo-doxorubicin, daunorubicin and 4-demethoxydaunorubicin (i.e. idarubicin).

A particularly preferred anthracycline glycoside is doxorubicin.

Any physiologically acceptable salt of the anthracycline glycoside may be used for preparing the solution of the invention. Examples of suitable salts may be, for instance, the salts with mineral inorganic acids such as hydrochloric, hydrobromic, sulfuric, phosphoric, nitric and the like, and the salts with certain organic acids such as acetic, succinic, tartaric, ascorbic, citric, glutammic, benzoic, methanesulfonic, ethanesulfonic and the like. The salt with hydrochloric acid is a particularly preferred salt, especially when the anthracycline glycoside is doxorubicin.

Any solvent which is physiologically acceptable and which is able to dissolve the anthracycline glycoside salt may be used. The solution of the invention may also contain one or more additional components such as a co-solubilizing agent (which may be the same as a solvent), a tonicity adjustment agent and a preservative. Examples of solvents, co-solubilizing agents, tonicity adjustment agents and preservatives which can be used for the preparation of the anthracycline glycoside solutions of the invention are hereunder reported.

Suitable solvents and co-solubilizing agents may be, for instance, water; physiological saline; aliphatic amides, e.g. N,N-dimethylacetamide, N-hydroxy-2-ethyl-lactamide and the like; alcohols, e.g. ethanol, benzyl alcohol and the like; glycols and polyalcohols, e.g. propyleneglycol, glycerin and the like; esters of polyalcohols, e.g. diacetine, triacetine and the like; polyglycols and polyethers, e.g. polyethyleneglycol 400, propyleneglycol methylethers and the like; dioxolanes, e.g. isopropylidenglycerin and the like; dimethylisosorbide; pyrrolidone derivatives, e.g. 2-pyrrolidone, N-methyl-2-pyrrolidone, polyvinylpyrrolidone (co-solubilizing agent only) and the like; polyoxyethylenated fatty alcohols, e.g. Brij® and the like; esters of polyoxyethylenated fatty acids, e.g. Cremophor®, Myrj® and the like; polysorbates, e.g. Tweens®; polyoxyethylene derivatives of polypropyleneglycols, e.g. Pluronics®.

A particularly preferred co-solubilizing agent is polyvinylpyrrolidone.

Suitable tonicity adjustment agents may be, for instance, physiologically acceptable inorganic chlorides, e.g. sodium chloride, dextrose, lactose, mannitol and the like.

Preservatives suitable for physiological administration may be, for instance, esters of para-hydroxybenzoic acid (e.g., methyl, ethyl, propyl and butyl esters, or mixtures of them), chlorocresol and the like.

The above mentioned solvents and co-solubilizing agents, tonicity adjustment agents and preservatives can be used alone or as a mixture of two or more of them.

Examples of preferred solvents are water, ethanol, polyethyleneglycol and dimethylacetamide as well as mixtures in various proportions of these solvents. Water is a particularly preferred solvent.

To adjust the pH within the range of from 2.5 to about 5.0 a physiologically acceptable acid may be added as desired. The acid may be any physiologically acceptable acid, e.g., an inorganic mineral acid such as hydrochloric, hydrobromic, sulfuric, phosphoric, nitric and the like, or an organic acid such as acetic, succinic, tartaric, ascorbic, citric, glutammic, benzoic, methanesulphonic, ethanesulfonic and the like, or also an acidic physiologically acceptable buffer solution, e.g., a chloride buffer, an acetate buffer, a phosphate buffer and the like.

For obtaining pH values from about 5 to about 5.5 the addition of the acid is not, usually, necessary, but only addition of a physiologically acceptable buffer solution, e.g., one of those indicated above, may be required, as desired.

For obtaining pH values from about 5.5 to 6.5 the addition of a physiologically acceptable alkalinizing agent, such as sodium hydroxide, a mono, di- or triethanolamine or the like, or, preferably, buffer solution such as a phosphate buffer, a TRIS buffer or the like is required.

The preferred range of pH for the ready-to-use solution of the invention is from 2.5 to 5.5, in particular from about 3 to about 5.2, a pH of about 3 and a pH of about 5 being particularly preferred values.

In the solutions of the invention the concentration of the anthracycline glycoside may vary within broad ranges, preferably, from 0.1 mg/ml to 100 mg/ml, in particular from 0.1 mg/ml to 50 mg/ml, most preferably from 1 mg/ml to 20 mg/ml.

The preferred ranges of concentration may be slightly different for different anthracycline glycosides. Thus, for example, preferred concentrations for doxorubicin are from about 2 mg/ml to about 50 mg/ml, preferably from 2 mg/ml to 20 mg/ml, particularly appropriate values being 2 mg/ml and 5 mg/ml. Similar concentrations are preferred also for 4'-epi-doxorubicin, 4'-desoxy-doxorubicin and 4'-desoxy-4'-iodo-doxorubicin. Preferred ranges of concentration for daunorubicin and 4-demethoxy-daunorubicin are from 0.1 mg/ml to 50 mg/ml, preferably from 1 mg/ml to 20 mg/ml, concentrations of 1 mg/ml and 5 mg/ml being particularly appropriate.

Suitable packaging for the anthracycline glycoside solutions may be all approved containers intended for parenteral use, such as plastic and glass containers, ready-to-use syringes and the like. Preferably the container is a sealed glass container, e.g. a vial or an ampoule.

According to a particularly preferred feature of the invention, there is provided a sterile, pyrogen-free, doxorubicin solution which consists essentially of a physiologically acceptable salt of doxorubicin dissolved in a physiologically acceptable solvent therefor, which has not been reconstituted from a lyophilizate and which has a pH of from 2.5 to 6.5.

In the above indicated preferred feature of the invention the physiologically acceptable salt of doxorubicin may be, e.g. the salt with a mineral inorganic acid such as hydrochloric, hydrobromic, sulfuric, phosphoric, nitric and the like, or the salt with an organic acid such as acetic, succinic, tartaric, ascorbic, citric, glutammic, benzoic, methanesulfonic, ethanesulfonic and the like. The hydrochloride salt is a particularly preferred salt.

For the solution hereabove indicated as a preferred feature of the invention suitable solvents, co-solubilizing agents, tonicity adjustment agents and preservatives may be the same as those previously recited in this specification. Water is a particularly preferred solvent.

Also, the physiologically acceptable acid which may be added to adjust the pH to from 2.5 to about 5, if desired, and the alkanilizing agent which may be added to adjust the pH, if desired, to a value from about 5.5 to 6.5 may be one of those previously specified. When it is desired to adjust the pH of the above said preferred solution to a value of from 2.5 to about 5, hydrochloric acid is an especially preferred acid. Preferred pH values for the above said preferred solutions of the invention are from 2.5 to 5.5, in particular from about 3 to about 5.2, the pH values of 3 and 5 being especially preferred.

Though the concentration of doxorubicin in the above preferred feature may vary within the broad range from 0.1 mg/ml to 100 mg/ml, preferred concentrations are from 2 mg/ml to 50 mg/ml, most preferably from 2 mg/ml to 20 mg/ml: examples of especially preferred concentrations of doxorubicin are 2 mg/ml and 5 mg/ml.

The invention also provides a process for producing a sterile, pyrogen-free anthracycline glycoside solution with a pH of from 2.5 to 6.5, which process comprises dissolving a physiologically acceptable salt of the anthracycline glycoside, which salt is not in the form of a lyophilizate, in a physiologically acceptable solvent therefor; optionally adding a physiologically acceptable acid or buffer to adjust the pH within the said range as desired; and passing the resulting solution through a sterilising filter.

One or more additional components such as co-solubilizing agents, tonicity adjustment agents and preservatives, for instance of the kind previously specified, may be added to the solution prior to passing the solution through the sterilising filter.

With the solutions of the invention it is possible to obtain compositions having a very high concentration of the anthracycline glycoside active substance even at 50 mg/ml and more. This constitutes a great advantage over the presently available lyophilized preparates wherein high concentrations of anthracycline glycoside can only be obtained with difficulty because of solubilization problems encountered in reconstitution, mainly with saline. The presence of the excipient, e.g. lactose, in the lyophilized cake, and its generally high proportion in respect of the active substance, even up to 5 parts of excipient per part of active substance, has a negative effect on solubilization so that difficulties may arise in obtaining dissolution of the lyophilized cake, especially for concentrations of anthracycline glycoside higher than 2 mg/ml.

The solutions of the invention are characterized by a good stability. Solutions in various solvents and with different pH's and concentrations have been found to be stable for long periods at temperatures accepted for the storage of pharmaceutical preparations. This is illustrated in the Examples which follow.

Owing to the well known anti-tumor activity of the anthracycline glycoside active drug substance, the pharmaceutical compositions of the invention are useful for treating tumors in both human and animal hosts. Examples of tumors that can be treated are, for instance, sarcomas, including osteogenic and soft tissue sarcomas, carcinomas, e.g., breast-, lung-, bladder-, thyroid-, prostate- and ovarian carcinoma, lymphomas, including Hodgkin and non-Hodgkin lymphomas, neuroblastoma, melanoma, myeloma, Wilms tumor, and leukemias, including acute lymphoblastic leukemia and acute myeloblastic leukemia. Examples of specific tumours that can be treated are Moloney sarcoma Virus, Sarcoma 180 Ascites, solid Sarcoma 180, gross transplantable leukemia, L 1210 leukemia and lymphocytic P 388 leukemia. Thus, according to the invention there is also provided a method of inhibiting the growth of a tumour, in particular one of those indicated above, which comprises administering to a host suffering from said tumour an injectable solution according to the invention containing the active drug substance in an amount sufficient to inhibit the growth of said tumour. The injectable solutions of the invention are administered b rapid intravenous injection or infusion according to a variety of possible dose schedules. Suitable dose schedule for doxorubicin may be, for example, of 60 to 75 mg of active drug substance per m^2 of body surface given as a single rapid infusion and repeated at 21 days; an alternative schedule may be of 30 mg/m^2 day by intravenous route for 3 days, every 25 days. Suitable dosages for 4'-epi-doxorubicin and 4 '-desoxy-doxorubicin may be, for instance, of 75 to 90 mg/m^2 given in a single infusion to be repeated at 21 days, and similar dosages may be useful also for 4 '-desoxy-4 '-iodo-doxorubicin. Idarubicin, i.e. 4-demethoxy-daunorubicin, may be. e.g., administered intravenously at a single dose of 13–15 mg//m^2 ever, 21 days in the treatment of solid tumours, while in the treatment of leukemias a preferred dose schedule is, e.g., of 10–12 mg/m^2 day by intravenous route for 3 days, to be repeated every 15–21 days; similar dosages may be, e.g., followed also for daunorubicin.

The following examples illustrate but do not limit in any way the invention.

With reference to the examples,the stability controls on the ready-to-use solutions were carried out by means of high performance liquid chromatography (HPLC), at the following

Liquid chromatograph	Varian model 5010
Spectrophotometric detector	Knauer model 8700
Integrating recorder	Varian model CDS 401
Injection valve	Rheodyne model 7125 fitted with a 10 mcl sample loop
Chromatographic column	Waters μ-Bondapak C18 (length = 300 mm; inner diameter = 3.9 mm; average particle size = 10 mcm)
Column temperature	ambient (about 22° C. ± 2° C.)
Mobile phase	water : acetonitrile (69:31 v/v) adjusted to pH 2 with phosphoric acid, filtered (sintered glass filter, 1 mcm or finer porosity) and deaerated
Mobile phase flow rate	1.5 ml/min
Analytical wavelength	254 ± 1 nm
Integrating recorder sensitivity	512
Chart speed	1 cm/min

At these conditions, the peak of the anthracycline glycoside showed a retention time of about 6 minutes. The obtained results are reported in the Tables accompanying the examples.

The extrapolation of the analytical data in order to determine the time when the 90% of the initial assay could be expected (t_{90} value) was made following an Arrhenius plot.

This procedure of analytical data treatment is well known and widely used and described in the art: see, e.g., Chemical Stability of Pharmaceuticals, Kennet A. Connors, Gordon L. Amidon, Lloyd Kennon, Publ. John Wiley and Sons, New York, N.Y., 1979.

The term "teflon" refers to "Teflon™".

EXAMPLE 1

Composition	for 80 vials	(for 1 vial)
Doxorubicin.HCl	0.8 g	(10 mg)
Water for injections q.s. to	0.4 l	(5 ml)

Doxorubicin.HCl (0.80 g) was dissolved in 90 percent of the amount of water for injections, de-aerated by nitrogen bubbling. The pH of the solution was not adjusted. Further de-aerated water for injections was then added to bring the solution to its final volume (0.40 1).

The solution was filtered through a 0.22μ microporous membrane under nitrogen pressure. Volumes of 5 ml of the solution were distributed into type I-colourless glass vials having 5/7 ml capacity. The vials were then closed with chlorobutyl teflon-faced rubber stoppers and sealed with aluminium caps.

The stability of the solutions in the vials was tested. The vials were stored at temperatures of 55° C., 45° C. and 35° C. (accelerated stability controls) and at 4° C. for up to 3 weeks (550° C.), 4 weeks (45° C. and 35° C.) and 12 weeks (4° C.).

The stability data obtained, using high performance liquid chromatography (HPLC) for the determination of potency, are reported in the following Table 1:

TABLE 1

INITIAL VALUES
Concentration:1.994 mg/ml pH = 5.2
Relative % Assay: 100.0

	TEMPERATURE							
	4° C.		35° C.		45° C.		55° C.	
TIME (weeks)	Conc. mg/ml	Rel.% Assay	Conc. mg/ml	Rel.% Assay	Conc. mg/ml	Rel.% Assay	Conc. mg/ml	Rel.% Assay
1	1.992	99.9	1.917	96.1	1.768	88.7	1.493	75.0
2			1.843	92.4	1.618	81.1	1.166	58.5
3			1.774	89.0	1.506	75.5	0.830	41.6
4	1.974	99.0	1.720	86.3	1.393	69.9		
12	1.980	99.3						

t_{90} (days) extrapolated according to Arrhenius equation:
t_{90} at 4° C. = 815 days
t_{90} at 8° C. = 480 days

Similar stability data can be observed also for analogous solutions containing either doxorubicin hydrochloride at 5 mg/ml concentration, or 4'-epi-doxorubicin, 4'-desoxy-doxorubicin, 4'-desoxy-4'-iodo-doxorubicin, daunorubicin or 4-demethoxy-daunorubicin, as hydrochloride salts, at both 2 mg/ml and 5 mg/ml concentration.

EXAMPLE 2

Composition	for 80 vials	(for 1 vial)
Doxorubicin.HCl	0.8 g	(10 mg)
Hydrochloric acid 0.1N q.s. to	pH = 3	(pH = 3)
Water for injections q.s. to	0.4 l	(5 ml)

Doxorubicin.HCl (0.8 g) was dissolved in 90 percent of the amount of water for injections, de-aerated by nitrogen bubbling. The hydrochloric acid was then added dropwise to adjust the pH of the solution to. 3. Further de-aerated water for injections was then added to bring the solution to its final volume (0.4 1).

The solution was filtered through a 0.22μ microporous membrane under nitrogen pressure. Volumes of 5 ml of the solution were distributed into type I-colourless glass vials

having 5⅓ ml capacity. The vials were then closed with chlorobutyl teflon-faced rubber stoppers and sealed with aluminium caps.

The stability of the solutions in the vials was tested. The vials were stored at temperatures of 55° C., 45° C. and 35° C. (accelerated stability controls) and at 4° C. for up to 3 weeks (55° C.), 4 weeks (45° C. and 35° C.) and 12 weeks (4° C.).

The stability data obtained, using high performance liquid chromatography (HPLC) for the determination of potency, are reported in the following Table 2:

TABLE 2

INITIAL VALUES
Concentration:1.992 mg/ml pH = 3.0
Relative % Assay: 100.0

	TEMPERATURE							
	4° C.		35° C.		45° C.		55° C.	
TIME (weeks)	Conc. mg/ml	Rel.% Assay	Conc. mg/ml	Rel.% Assay	Conc. mg/ml	Rel.% Assay	Conc. mg/ml	Rel.% Assay
1	1.995	100.2	1.952	98.0	1.919	96.3	1.493	75.0
2			1.889	94.8	1.851	92.9	1.036	51.9
3			1.876	94.2	1.565	78.6	0.730	36.7
4	1.979	99.4	1.808	90.8	1.393	69.9		
12	1.972	99.0						

t_{90} (days) extrapolated according to Arrhenius equation:
t_{90} at 4° C. = 3970 days
t_{90} at 8° C. = 2000 days

Similar stability data can be observed also for analogous solutions containing either doxorubicin hydrochloride at 5 mg/ml concentration, or 4'-epi-doxorubicin, 4'-desoxy-doxorubicin, 4'-desoxy-4'-iodo-doxorubicin, daunorubicin or 4-demethoxy-daunorubicin, as hydrochloride salts, at both 2 mg/ml and 5 mg/ml concentration.

EXAMPLE 3

Composition	for 80 vials	(for 1 vial)
Doxorubicin.HCl	8.0 g	(100 mg)
Hydrochloric acid 0.1N q.s. to	pH = 3	(pH = 3)
Water for injections q.s. to	0.4 l	(5 ml)

Doxorubicin.HCl (8.0 g) was dissolved in 90 percent of the amount of water for injections, de-aerated by nitrogen bubbling. The hydrochloric acid was then added dropwise to adjust the pH of the solution to 3. Further de-aerated water for injections was then added to bring the solution to its final volume (0.4 1).

The solution was filtered through a 0.22μ microporous membrane under nitrogen pressure. Volumes of 5 ml of the solution were distributed into type I-colourless glass vials having 5⅓ ml capacity. The vials were then closed with chlorobutyl teflon-faced rubber stoppers and sealed with aluminium caps.

The stability of the solutions in the vials was tested. The vials were stored at temperatures of 55° C., 45° C. and 35° C. (accelerated stability controls) and at 4° C. for up to 3 weeks (55° C.), 4 weeks (45° C. and 35° C.) and 12 weeks (4° C.).

The stability data obtained, using high performance liquid chromatography (HPLC) for the determination of potency, are reported in the following Table 3:

TABLE 3

INITIAL VALUES
Concentration:20.06 mg/ml pH = 2.95
Relative % Assay: 100.0

	TEMPERATURE							
	4° C.		35° C.		45° C.		55° C.	
TIME (weeks)	Conc. mg/ml	Rel.% Assay	Conc. mg/ml	Rel.% Assay	Conc. mg/ml	Rel.% Assay	Conc. mg/ml	Rel.% Assay
1	20.06	100.0	19.56	97.5	17.84	88.9	12.31	61.4
2			18.87	94.1	15.61	77.8	7.09	35.3
3			18.24	90.9	13.41	66.8	3.13	15.6
4	19.91	99.2	17.51	87.3	11.07	55.2		
12	19.80	98.7						

t_{90} (days) extrapolated according to Arrhenius equation:
t_{90} at 4° C. = 3700 days
t_{90} at 8° C. = 1780 days

Similar stability data can be observed for analogous solutions containing 4'-epi-doxorubicin or 4'-desoxy-doxorubicin, as hydrochloride salts, at the same 20 mg/ml concentration.

EXAMPLE 4

Composition	for 80 vials	(for 1 vial)
Doxorubicin.HCl	0.80 g	(10.0 mg)
Polyvinylpyrrolidone	20.00 g	(250.0 mg)
Water for injections q.s. to	0.40 l	(5.0 ml)

Doxorubicin.HCl (0.80 g) was dissolved in 90 percent of the amount of water for injections, de-aerated by nitrogen bubbling. The pH of the solution was not adjusted. Polyvinylpyrrolidone was added and dissolved under stirring and nitrogen bubbling. Further de-aerated water for injections was then added to bring the solution to its final volume (0.40 1).

The solution was filtered through a 0.22μ microporous membrane under nitrogen pressure. Volumes of 5 ml of the solution were distributed into type I-colourless glass vials having 5/7 ml capacity. The vials were then closed with chlorobutyl teflon-faced rubber stoppers and sealed with aluminium caps.

The stability of the solutions in the vials was tested. The vials were stored at temperatures of 55° C., 45° C. and 35° C. (accelerated stability controls) and at 4° C. for up to 3 weeks (55° C.), 4 weeks (45° C. and 35° C.) and 8 weeks (4° C.).

The stability data obtained, using high performance liquid chromatography (HPLC) for the determination of potency, are reported in the following Table 4:

TABLE 4

INITIAL VALUES
Concentration:1.986 mg/ml pH = 4.6
Relative % Assay: 100.0

	TEMPERATURE							
	4° C.		35° C.		45° C.		55° C.	
TIME (weeks)	Conc. mg/ml	Rel.% Assay	Conc. mg/ml	Rel.% Assay	Conc. mg/ml	Rel.% Assay	Conc. mg/ml	Rel.% Assay
1	1.984	99.9	1.928	97.1	1.797	90.5	1.605	80.8
2			1.847	93.0	1.616	81.4	1.293	65.1
3			1.828	92.0	1.527	76.9	1.018	51.3
4	1.928	97.1	1.797	90.5	1.403	70.7		
8	1.989	100.1						

t_{90} (days) extrapolated according to Arrhenius equation:
t_{90} at 4° C. = 1460 days
t_{90} at 8° C. = 835 days

Similarr stability data can be observed also for analogous solutions containing either doxorubicin hydrochloride at 5 mg/ml concentration, or 4'-epi-doxorubicin, 4'-desoxy-doxorubicin, 4'-desoxy-4'- iodo-doxorubicin, daunorubicin or 4-demethoxy-daunorubicin, as hydrochloride salts, at both 2 mg/ml and 5 mg/ml concentration.

EXAMPLE 5

Composition	for 80 vials	(for 1 vial)
Doxorubicin.HCl	0.800 g	(10.00 mg)
N,N-Dimethylacetamide	0.060 l	(0.75 ml)
Propylene glycol	0.048 l	(0.60 ml)
Ethanol	0.012 l	(0.15 ml)
Hydrochloric acid 0.1N q.s. to	pH = 3	(pH = 3)
Water for injections q.s. to	0.400 l	(5.00 ml)

Doxorubicin.HCl (0.800 g) was dissolved in 90 percent of the amount of water for injections, de-aerated by nitrogen bubbling. N,N-dimethylacetamide, propylene glycol and ethanol were subsequently added under stirring and nitrogen bubbling. The hydrochloric acid was then added dropwise to adjust the pH of the solution to 3. Further de-aerated water for injections was then added to bring the solution to its final volume (0.400 1).

The solution was filtered through a 0.22μ microporous membrane under nitrogen pressure. Volumes of 5 ml of the solution were distributed into type I-colourless glass vials having 5/7 ml capacity. The vials were then closed with chlorobutyl teflon-faced rubber stoppers and sealed with aluminium caps.

The stability of the solutions in the vials was tested. The vials were stored at temperatures of 55° C., 45° C. and 35° C. (accelerated stability controls) and at 4° C. for up to 3 weeks (55° C.), 4 weeks (45° C. and 35° C.) and 8 weeks (4° C.).

The stability data obtained, using high performance liquid chromatography (HPLC) for the determination of potency, are reported in the following Table 5:

TABLE 5

INITIAL VALUES
Concentration:2.000 mg/ml pH = 3.03
Relative % Assay: 100.0

	TEMPERATURE							
	4° C.		35° C.		45° C.		55° C.	
TIME (weeks)	Conc. mg/ml	Rel.% Assay	Conc. mg/ml	Rel.% Assay	Conc. mg/ml	Rel.% Assay	Conc. mg/ml	Rel.% Assay
1			1.892	94.6	1.735	86.7	1.495	74.7
2	1.993	99.7	1.927	96.4	1.624	81.2	1.212	60.6
3			1.908	95.4	1.432	71.6	1.032	51.6
4	2.00	100.0	1.863	93.2	1.266	63.3		
8	1.960	98.0						

t_{90} (days) extrapolated according to Arrhenius equation:
t_{90} at 4° C. = 4360 days
t_{90} at 8° C. = 2200 days

Similar stability data can be observed also for analogous solutions containing either doxorubicin hydrochloride at 5 mg/ml concentration, or 4'-epi-doxorubicin, 4'-desoxy-doxorubicin, 4'-desoxy-iodo-doxorubicin, daunorubicin or 4-demethoxy-daunorubicin, hydrochloride salts, at both 2 mg/ml and 5 mg/ml concentration.

EXAMPLE 6

Composition	for 80 vials	(for 1 vial)
Doxorubicin.HCl	0.8 g	(10.0 mg)
Polyvinylpyrrolidone	20.0 g	(250.0 mg)
Hydrochloric acid 0.1N q.s. to	pH = 3	(pH = 3)
Water for injections q.s. to	0.4 l	(5.0 ml)

Doxorubicin.HCl (0.8 g) was dissolved in 90 percent of the amount of water for injections, de-aerated by nitrogen bubbling. Polyvinylpyrrolidone was added and dissolved under stirring and nitrogen bubbling. The hydrochloric acid was then added dropwise to adjust the pH of the solution to 3. Further de-aerated water for injections was then added to bring the solution to its final volume (0.4 1).

The solution was filtered through a 0.22μ microporous membrane under nitrogen pressure. Volumes of 5 ml of the solution were distributed into type I-colourless glass vials

The solution was filtered through a 0.22μ microporous membrane under nitrogen pressure. Volumes of 5 ml of the solution were distributed into type I-colourless glass vials having 5/7 ml capacity. The vials were then closed with chlorobutyl teflon-faced rubber stoppers and sealed with aluminium caps.

The stability of the solutions in the vials was tested. The vials were stored at temperatures of 55° C., 45° C. and 35° C. (accelerated stability controls) and at 4° C. for up to 3 weeks (55° C.), 4 weeks (45° C. and 35° C.) and 8 weeks (4° C.).

The stability data obtained, using high performance liquid chromatography (HPLC) for the determination of potency, are reported in the following Table 6;

TABLE 6

INITIAL VALUES
Concentration: 1.973mg/ml pH = 2.71
Relative % Assay: 100.0

	TEMPERATURE							
	4° C.		35° C.		45° C.		55° C.	
TIME (weeks)	Conc. mg/ml	Rel.% Assay	Conc. mg/ml	Rel.% Assay	Conc. mg/ml	Rel.% Assay	Conc. mg/ml	Rel.% Assay
1	2.028	102.8	1.944	98.5	1.791	90.8	1.477	74.9
2			1.885	95.5	1.582	80.2	0.972	49.3
3			1.840	93.2	1.402	71.0	0.632	32.0
4	1.913	97.0	1.853	93.9	1.273	64.5		
8	1.972	99.9						

t_{90} (days) extrapolated according to Arrhenius equation:
t_{90} at 4° C. = 5560 days
t_{90} at 8° C. = 2670 days

Similar stability data can be observed also for analogous solutions containing either doxorubicin hydrochloride at 5 mg/ml concentration, or 4'-epi-doxorubicin, 4'-desoxy-doxorubicin, 4'-desoxy-4'-iodo-doxorubicin, daunorubicin or 4-demethoxy-daunorubicin, as hydrochloride salts, at both 2 mg/ml and 5 mg/ml concentration.

EXAMPLE 7

Composition	for 80 vials	(for 1 vial)
Doxorubicin.HCl	8.00 g	(100.0 mg)
N,N-Dimethylacetamide	0.12 l	(1.5 ml)
Hydrochloric acid 0.1N q.s. to	pH = 3	(pH = 3)
Water for injections q.s. to	0.40 l	(5.0 ml)

Doxorubicin.HCl (8.00 g) was dissolved in 90 percent of the amount of water for injections, de-aerated by nitrogen bubbling. N,N-dimethylacetamide was added under stirring and nitrogen bubbling. The hydrochloric acid was then added dropwise to adjust the pH of the solution to 3. Further de-aerated water for injections was then added to bring the solution to its final volume (0.40 1).

The solution was filtered through a 0.22μ microporous membrane under nitrogen pressure. Volumes of 5 ml of the solution were distributed into type I-colourless glass vials having 5/7 ml capacity. The vials were then closed with chlorobutyl teflon-faced rubber stoppers and sealed with aluminium caps.

The stability of the solutions in the vials was tested. The vials were stored at temperatures of 55° C., 45° C. and 35° C. (accelerated stability controls) and at 4° C. for up to 3 weeks (55° C.), 4 weeks (45° C. and 35° C.) and 8 weeks (4° C.).

The stability data obtained, using high performance liquid chromatography (HPLC) for the determination of potency, are reported in the following Table 7:

TABLE 7

INITIAL VALUES
Concentration:19.32 mg/ml pH = 2.96
Relative % Assay: 100.0

	TEMPERATURE							
	4° C.		35° C.		45° C.		55° C.	
TIME (weeks)	Conc. mg/ml	Rel.% Assay	Conc. mg/ml	Rel.% Assay	Conc. mg/ml	Rel.% Assay	Conc. mg/ml	Rel.% Assay
1	20.1	103.5	19.14	99.1	17.34	89.8	15.57	80.6
2			19.20	99.4	15.77	81.6	12.94	67.0
3			18.06	93.5	14.85	76.9	11.61	60.1
4	20.03	103.7	17.81	92.2	13.78	71.3		
8	19.99	103.5						

t_{90} (days) extrapolated according to Arrhenius equation:
t_{90} at 4° C. = 1310 days
t_{90} at 8° C. = 770 days

Similar stability data can be observed for analogous solutions containing 4'-epi-doxorubicin or 4'-desoxy-doxorubicin, as hydrochloride salts, at the same 20 mg/ml concentration.

EXAMPLE 8

Composition	for 80 vials	(for 1 vial)
Doxorubicin.HCl	0.80 g	(10.0 mg)
Ethanol	0.12 l	(1.5 ml)
Hydrochloric acid 0.1 N q.s. to	pH = 3	(pH = 3)
Water for injections q.s. to	0.40 l	(5.0 ml)

Doxorubicin.HCl (0.80g) was dissolved in 90 percent of the amount of water for injections, de-aerated by nitrogen bubbling. Ethanol was added under stirring and nitrogen bubbling. Hydrochloric acid 0.1 N was then added dropwise to adjust the pH of the solution to 3. De-aerated water for injections was finally added to bring the solution to its final volume (0.40 1).

The solution was filtered through a 0.22μ microporous membrane under nitrogen pressure. Volumes of 5 ml of the solution were distributed into type I-colourless glass vials having 5/7 ml capacity. The vials were then closed with chlorobutyl teflon-faced rubber stoppers and sealed with aluminium caps.

The stability of the solutions in the vials was tested. The vials were stored at temperatures of 55° C., 45° C. and at 35° C. (accelerated stability controls) and at 4° C. for up to 3 weeks (55° C.), 4 weeks (45° C. and 35° C.) and 12 weeks (4° C.).

The stability data obtained, using high performance liquid chromatography (HPLC) for the determination of potency, are reported in the following Table 8.

TABLE 8

INITIAL VALUES
Concentration:1.979 mg/ml pH = 3.11
Relative % Assay: 100.0

	TEMPERATURE							
	4° C.		35° C.		45° C.		55° C.	
TIME (weeks)	Conc. mg/ml	Rel.% Assay	Conc. mg/ml	Rel.% Assay	Conc. mg/ml	Rel.% Assay	Conc. mg/ml	Rel.% Assay
1	2.010	101.6	1.965	99.3	1.947	98.4	1.750	88.4
2			1.957	98.9	1.910	96.5	1.645	83.1
3			1.895	95.8	1.737	87.8	1.356	68.5
4	1.927	97.3	1.818	91.9	1.678	84.8		
12	1.939	97.9						

t_{90} (days) extrapolated according to Arrhenius equation:
t_{90} at 4° C. = 1270 days
t_{90} at 8° C. = 780 days

Similar stability data can be observed also for analogous solutions containing either doxorubicin hydrochloride at 5 mg/ml concentration, or 4'-epi-doxorubicin, 4'-desoxy-doxorubicin, 4'-desoxy-4'-iodo-doxorubicin, daunorubicin or 4-demethoxy-daunorubicin, as hydrochloride salts, at both 2 mg/ml and 5 mg/ml concentration.

EXAMPLE 9

Composition	for 80 vials	(for 1 vial)
Doxorubicin.HCl	8.000 g	(100.00 mg)
N,N-Dimethylacetamide	0.060 l	(0.75 ml)
Propylene glycol	0.048 l	(0.60 ml)
Ethanol	0.012 l	(0.15 ml)
Hydrochloric acid 0.1N q.s. to	pH = 3	(pH = 3)
Water for injections q.s. to	0.400 l	(5.00 ml)

Doxorubicin.HCl (8.000 g) was dissolved in 90 percent of the amount of water for injections, de-aerated by nitrogen bubbling. N,N-dimethylacetamide, propylene glycol and ethanol were subsequently added under stirring and nitrogen bubbling. The hydrochloric acid was then added dropwise to adjust the pH of the solution to 3. Further de-aerated water for injections was then added to bring the solution to its final volume (0.400 1).

The solution was filtered through a 0.22μ microporous membrane under nitrogen pressure. Volumes of 5 ml of the solution were distributed into type I-colourless glass vials having 5⁄7 ml capacity. The vials were then closed with chlorobutyl teflon-faced rubber stoppers and sealed with aluminium caps.

The stability of the solutions in the vials was tested. The vials were stored at temperatures of 55° C., 45° C. and 35° C. (accelerated stability controls) and at 4° C. for up to 3 weeks (55° C.), 4 weeks (45° C. and 35° C.) and 8 weeks (4° C.).

The stability data obtained, using high performance liquid chromatography (HPLC) for the determination of potency, are reported in the following Table 9:

TABLE 9

INITIAL VALUES
Concentration:20.07 mg/ml pH = 2.99
Relative % Assay: 100.0

	TEMPERATURE							
	4° C.		35° C.		45° C.		55° C.	
TIME (weeks)	Conc. mg/ml	Rel.% Assay	Conc. mg/ml	Rel.% Assay	Conc. mg/ml	Rel.% Assay	Conc. mg/ml	Rel.% Assay
1			19.14	95.4	17.81	88.7	14.84	73.9
2	19.97	99.5	19.07	95.0	16.27	81.1	12.36	61.6
3			18.08	90.1	14.62	72.9	10.04	50.0
4	20.06	99.9	18.03	89.8	13.20	65.8		
8	19.69	98.1						

t_{90} (days) extrapolated according to Arrhenius equation:
t_{90} at 4° C. = 846 days
t_{90} at 8° C. = 505 days

Similar stability data can be observed for analogous solutions containing 4'-epi-doxorubicin or 4'-desoxy-doxorubicin, as hydrochloride salts, at the same 20 mg/ml concentration.

EXAMPLE 10

Composition	for 80 vials	(for 1 vial)
Doxorubicin.HCl	8.0 g	(100.0 mg)
Polyvinylpyrrolidone	20.0 g	(250.0 mg)
Hydrochloric acid 0.1N q.s. to	pH = 3	(pH = 3)
Water for injections q.s. to	0.4 l	(5.0 ml)

Doxorubicin.HCl (8.0 g) was dissolved in 90 percent of the amount of water for injections, de-aerated by nitrogen bubbling. Polyvinylpyrrolidone was added and dissolved under stirring and nitrogen bubbling. The hydrochloric acid was then added dropwise to adjust the pH of the solution to 3. Further de-aerated water for injections was then added to bring the solution to its final volume (0.4 1).

The solution was filtered through a 0.22μ microporous membrane under nitrogen pressure. Volumes of 5 ml of the solution were distributed into type I-colourless glass vials having 5/7 ml capacity. The vials were then closed with chlorobutyl teflon-faced rubber stoppers and sealed with aluminium caps.

The stability of the solutions in the vials was tested. The vials were stored at temperatures of 55° C., 45° C. and 35° C. (accelerated stability controls) and at 4° C. for up to 3 weeks (55° C.), 4 weeks (45°C. and 35° C.) and 8 weeks (4° C.).

The stability data obtained, using high performance liquid chromatography (HPLC) for the determination of potency, are reported in the following Table 10:

TABLE 10

INITIAL VALUES
Concentration: 19.57 mg/ml pH = 2.62
Relative % Assay: 100.0

	TEMPERATURE							
	4° C.		35° C.		45° C.		55° C.	
TIME (weeks)	Conc. mg/ml	Rel.% Assay	Conc. mg/ml	Rel.% Assay	Conc. mg/ml	Rel.% Assay	Conc. mg/ml	Rel.% Assay
1	19.54	99.9	19.11	97.6	16.88	86.2	12.48	63.8
2			18.43	94.2	14.13	72.2	6.00	30.7
3			18.02	92.1	11.57	59.1	2.61	13.3
4	19.58	100.1	17.36	88.7	9.23	47.2		
8	19.34	98.8						

t_{90} (days) extrapolated according to Arrhenius equation:
t_{90} at 4° C. = 2540 days
t_{90} at 8° C. = 1290 days

Similar stability data can be observed for analogous solutions containing 4'-epi-doxorubicin or 4'-desoxy-doxorubicin, as hydrochloride salts, at the same 20 mg/ml concentration.

EXAMPLE 11

Composition	for 80 vials	(for 1 vial)
Doxorubicin.HCl	0.80 g	(10.0 mg)
N,N-Dimethylacetamide	0.12 l	(1.5 ml)
Hydrochloric acid 0.1N q.s. to	pH = 3	(pH = 3)
Water for injections q.s. to	0.40 l	(5.0 ml)

Doxorubicin.HCl (0.80 g) was dissolved in 90% of the amount of water for injections, de-aerated by nitrogen bubbling. N,N-Dimethylacetamide was added under stirring and nitrogen bubbling. Hydrochloric acid 0.1N was then added dropwise to adjust the pH of the solution to 3. De-aerated water for injections was finally added to bring the solution to its final volume (0.40 1).

The solution was filtered through a 0.22μ microporous membrane under nitrogen pressure. Volumes of 5 ml of the solution were distributed into type I-colourless glass vials having 5/7 ml capacity. The vials were then closed with chlorobutyl teflon-faced rubber stoppers and sealed with aluminium caps.

The stability of the solutions in the vials was tested. The vials were stored at temperatures of 55° C., 45° C. and 35° C. (accelerated stability controls) and at 4° C. for up to 3 weeks (55° C.), 4 weeks (45° C. and 35° C.) and 8 weeks (4° C.).

The stability data obtained, using high performance liquid chromatography (HPLC) for the determination of potency, are reported in the following Table 11:

TABLE 11

INITIAL VALUES
Concentration: 1.826 mg/ml pH = 3.14
Relative % Assay: 100.0

	TEMPERATURE							
	4° C.		35° C.		45° C.		55° C.	
TIME (weeks)	Conc. mg/ml	Rel.% Assay	Conc. mg/ml	Rel.% Assay	Conc. mg/ml	Rel.% Assay	Conc. mg/ml	Rel.% Assay
1	1.830	100.2	1.812	99.2	1.784	97.7	1.605	87.9
2	1.818	99.6	1.781	97.5	1.554	85.1	1.292	70.8
3			1.743	95.4	1.409	77.2	1.018	55.7
4	1.823	99.8	1.734	95.0	1.369	75.0		
8	1.792	98.2						

t_{90} (days) extrapolated according to Arrhenius equation:
t_{90} at 4° C. = 5815 days
t_{90} at 8° C. = 2920 days

Similar stability data can be observed also for analogous solutions containing either doxorubicin hydrochloride at 5 mg/ml concentration, or 4'-epi-doxorubicin, 4'-desoxy-doxorubicin, 4'-epi-desoxy-4'-iodo-doxorubicin, daunorubicin or 4-demethoxy-daunorubicin, as hydrochloride salts, at both 2 mg/ml and 5 mg/ml concentration.

EXAMPLE 12

Composition	for 80 vials	(for 1 vial)
Doxorubicin.HCl	0.80 g	(10.0 mg)
Propylene glycol	0.12 l	(1.5 ml)
Hydrochloric acid 0.1N q.s. to	pH = 3	(pH = 3)
Water for injections q.s. to	0.40 l	(5.0 ml)

Doxorubicin.HCl (0.80 g) was dissolved in 90% of the amount of water for injections de-aerated by nitrogen bubbling. Propylene glycol was added under stirring and nitrogen bubbling. Hydrochloric acid 0.1 N was then added dropwise to adjust the pH of the solution to 3. De-aerated water for injections was finally added to bring the solution to its final volume (0.40 l).

The solution was filtered through a 0.22μ microporous membrane under nitrogen pressure. Volumes of 5 ml of the solution were distributed into type I-colourless glass vials having 5/7 ml capacity. The vials were then closed with chlorobutyl teflon-faced rubber stoppers and sealed with aluminium caps.

The stability of the solutions in the vials was tested. The vials were stored at temperatures of 55° C., 45° C. and 35° C. (accelerated stability controls) and at 4° C. for up to 3 weeks (55° C.), 4 weeks (45° C. and 35° C.) and 4 weeks (4° C.).

The stability data obtained, using high performance liquid chromatography (HPLC) for the determination of potency, are reported in the following Table 12:

TABLE 12

INITIAL VALUES
Concentration: 1.982 mg/ml pH = 3.11
Relative % Assay: 100.0

	TEMPERATURE							
	4° C.		35° C.		45° C.		55° C.	
TIME (weeks)	Conc. mg/ml	Rel.% Assay	Conc. mg/ml	Rel.% Assay	Conc. mg/ml	Rel.% Assay	Conc. mg/ml	Rel.% Assay
1	1.972	99.5	1.934	97.6	1.889	95.3	1.705	86.0
2			1.952	98.5	1.795	90.6	1.483	74.8
3			1.935	97.6	1.699	85.7	1.153	58.2
4	2.056	103.7	1.788	90.2	1.460	73.7		

t_{90} (days) extrapolated according to Arrhenius equation:
t_{90} at 4° C. = 1794 days
t_{90} at 8° C. = 1025 days

Similar stability data can be observed also for analogous solutions containing either doxorubicin hydrochloride at 5 mg/ml concentration, or 4'-epi-doxorubicin, 4'-desoxy-doxorubicin, 4'-desoxy-4'-iodo-doxorubicin, daunorubicin or 4-demethoxy-daunorubicin, as hydrochloride salts, at both 2 mg/ml 5 mg/ml concentration.

EXAMPLE 13

Composition	for 80 vials	(for 1 vial)
Doxorubicin.HCl	0.80 g	(10.0 mg)
Polyethylene glycol 400	0.12 l	(1.5 ml)
Hydrochloric acid 0.1N q.s. to	pH = 3	(pH = 3)
Water for injections q.s. to	0.40 l	(5.0 ml)

Doxorubicin.HCl (0.80 g) was dissolved in 90% of the amount of water for injections, de-aerated by nitrogen bubbling. Polyethylene glycol 400 was added under stirring and nitrogen bubbling. Hydrochloric acid 0.1 N was then added dropwise to adjust the pH of the solution to 3. De-aerated water for injections was finally added to bring the solution to its final volume (0.40 1).

The solution was filtered through a 0.22μ microporous membrane under nitrogen pressure. Volumes of 5 ml of the solution were distributed into type I-colourless glass vials having 5/7 ml capacity. The vials were then closed with chlorobutyl teflon-faced rubber stoppers and sealed with aluminium caps.

The stability of the solutions in the vials was tested. The vials were stored at temperatures of 55° C., 45° C. and 35° C. (accelerated stability controls) and at 4° C. for up to 3 weeks (55° C.), 4 weeks (45° C. and 35° C.) and 4 weeks (4° C.).

The stability data obtained, using high performance liquid chromatography (HPLC) for the determination of potency, are reported in the following Table 13:

TABLE 13

INITIAL VALUES
Concentration: 1.907 mg/ml pH = 3.07
Relative % Assay: 100.0

	TEMPERATURE							
	4° C.		35° C.		45° C.		55° C.	
TIME (weeks)	Conc. mg/ml	Rel.% Assay	Conc. mg/ml	Rel.% Assay	Conc. mg/ml	Rel.% Assay	Conc. mg/ml	Rel.% Assay
1	1.871	98.1	1.797	94.2	1.668	87.5	1.484	77.8
2			1.710	89.7	1.608	84.3	1.237	64.9
3			1.739	91.2	1.551	81.3	1.007	52.8
4	1.873	98.2	1.693	88.8	1.453	76.2		

t_{90} (days) extrapolated according to Arrhenius equation:
t_{90} at 4° C. = 1130 days
t_{90} at 8° C. = 680 days

Similar stability data can be observed also for analogous solutions containing either doxorubicin hydrochloride at 5mg/ml concentration, or 4'-epi-doxorubicin, 4'-desoxy-doxorubicin, 4'-desoxy-4'-iodo-doxorubicin, daunorubicin or 4-demethoxy-daunorubicin, as hydrochloride salts, at both 2 mg/ml and 5 mg/ml concentration.

EXAMPLE 14

Composition	for 80 vials	(for 1 vial)
Doxorubicin.HCl	0.8 g	(10 mg)
Hydrochloric acid 0.1N	pH = 3	(pH = 3)

-continued

Composition	for 80 vials	(for 1 vial)
q.s. to Water for injections q.s. to	0.4 l	(5 ml)

Doxorubicin.HCl (0.8 g) was dissolved in 90 percent of the amount of water for injections, de-aerated by nitrogen bubbling. The hydrochloric acid was then added dropwise to adjust the pH of the solution to 3. Further de-aerated water for injections was then added to bring the solution to its final volume (0.4 1).

The solution was filtered through a 0.22μ microporous membrane under nitrogen pressure. Volumes of 5 ml of the solution were distributed into type I-colourless glass vials having 5/7 ml capacity. The vials were then closed with chlorobutyl teflon-faced rubber stoppers and sealed with aluminium caps.

The stability of the solutions in the vials was tested. The vials were stored at temperatures of 4° C. and 8° C. for up to 6 months.

The stability data obtained, using high performance liquid chromatography (HPLC) for the determination of potency, are reported in the following Table 14:

TABLE 14

INITIAL VALUES
Concentration: 2.039 mg/ml pH = 3.06
Relative % Assay: 100.0

	TEMPERATURE			
	4° C.		8° C.	
TIME (months)	Conc. mg/ml	Rel.% Assay	Conc. mg/ml	Rel.% Assay
1	1.983	97.3	1.959	96.1
3	1.984	97.3	1.983	97.3
6	2.012	98.7	2.002	98.2

At the same conditions, similar stability data can be generally observed also for the other solutions mentioned in the preceding examples.

We claim:

1. A physiologically acceptable solution of anthracycline glycoside selected from the group consisting of idarubicin hydrochloride, doxorubicin hydrochloride and epirubicin hydrochloride dissolved in a physiologically acceptable aqueous solvent, having a pH adjusted to from 2.5 to 5.0 with a physiologically acceptable acid selected from the group consisting of hydrochloric acid, sulfuric acid, phosphoric acid, methane sulfonic acid, and tartaric acid, the concentration of said anthracycline glycoside being from 0.1 to 100 mg/ml, wherein said solution is contained in a sealed container.

2. The solution of claim 1 wherein said physiologically acceptable aqueous solvent is selected from the group consisting of water, ethanol, polyethylene glycol, dimethylacetamide, and mixtures thereof.

3. The solution of claim 1 wherein the physiologically acceptable aqueous solvent is water.

4. The solution of claim 1 wherein the concentration of the doxorubicin is from 0.1 to 50 mg/ml.

5. The solution of claim 4 wherein the concentration of doxorubicin is from 1 to 20 mg/ml.

6. The solution of claim 1 wherein the concentration of doxorubicin is about 2 mg/ml.

7. The solution of claim 1 wherein the concentration of doxorubicin is about 5 mg/ml.

8. A sealed container containing a stable, intravenously injectable, sterile, pyrogen-free doxorubicin solution which consists essentially of doxorubicin hydrochloride dissolved in a physiologically acceptable solvent therefore, wherein said solution has a pH adjusted to 2.71 to 3.14 with a physiologically acceptable acid and has a concentration of doxorubicin of from 0.1 to 100 mg/ml.

9. The anthracycline glycoside solution of claim 1, wherein said solution exhibits storage stability as a result of said pH being adjusted to the said pH range using said acids.

10. The container of claim 8, wherein said doxorubicin solution exhibits storage stability as a result of said pH being adjusted to the said pH range using said acids.

11. The solution of claim 1 wherein the concentration of anthracycline glycoside is about 1 mg/ml.

12. The solution of claim 11 wherein the physiologically acceptable acid is hydrochloric acid.

13. The solution of claim 12 wherein the anthracycline glycoside is idarubicin hydrochloride.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,107,285
DATED : August 22, 2000
INVENTOR(S) : Gaetano Gatti et al

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Title page,
Item [56], **Reference Cited,** U.S. PATENT DOCUMENTS; please insert
-- 3,803,124 4/1974 Arcamone et al. --;
FOREIGN PATENT DOCUMENTS please insert -- 3621844 A1 3/1987 Germany --;
please insert -- 1,291,037 1991/10/22 Canada --;
OTHER PUBLICATIONS; please insert the following references:
-- Beijnen et al. (1985), Stability of Anthracycline Antitumor Agents in Infusion Fluids," J. Parenteral Science and Technology, Vol. 39, pp. 220-222.

Daugherty et al. (1981), "Photolytic Destruction of Adriamycin," J. Pharm. Pharmacol. Vol.33, p. 556.

Dorr and Fritz (1980), "Doxorubicin," Cancer Chemotherapy Handbook, Elsevier, New York, pp. 388-401.

Flora et al. (1980), "The Loss of Paraben Preservatives During Freeze Drying," J. Pharm. Pharmacol., vol. 32, pp. 577-578.

Florence and Atwood (1981), "Physicochemical Principles of Pharmacy," MacMillan Press, London, p. 475.

Garnick et al. (1983), "Clinical Evaluation of Long-Term, Continuous Infusion Doxorubicin," Cancer Treatment Reports, vol. 67, pp. 133-142.

Henry, D. W. (1976), "Adriamycin," Cancer Chemotherapy, American Chemical Society Symposium Series, pp. 15-57.

Kaniewska, T. (1977), "A Study of Decomposition of Adriamycin," Pharmacia Polska, vol. 9, 539-542.

Ketchum et al. (1981), "Cost Benefit and Stability Study of Doxorubicin Following Reconstitution," Am. J. Intravenous Therapy & Clinical Nutrition, vol. 8, pp. 15-18.

Kristensen and Moller (1983), "Almen Farmaci II," Dansk Farmaceutforeigs Forlag, Kobenhavn, pp. 408, 442, 447.

Menozzi et al. (1984), "Self Association of Doxorubicin and Related Compounds in Aqueous Solution," J. Pharamaceutical Sciences, vol. 73, pp. 766-770.

Savlov et al. (1981), "Comparison of Doxorubicin With Cycloleucine in the treatment of Sarcomas," Cancer Treatment Sciences, vol. 65, pp. 21-27.

Trissell (1980), "Doxorubicin HCl," Handbook of Injectable Drugs, Third Ed. (American Society of Hospital Pharmacists, Bethesda, MD), pp. 131-132.

Williamson et al. (1980), "Doxorubicin Hydrochloride-Aluminium Interaction," Am. J. Hospital Pharmacy, vol. 40, p. 214.

Drug Topics, "Cancer Drug Danger," February 7, 1983, p. 99.

Gutteridge and Wilkins (1983), "Doxorubicin Degradation: Changes in Activity Compared by Bacterial Growth Inhibition and Free Radical-Dependent Damage to Deoxyribose," J. Biological Standardization, vol. 11, pp. 359-364.

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,107,285
DATED : August 22, 2000
INVENTOR(S) : Gaetano Gatti et al

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Akbiyik et al. (1979), "Total Lung Irradiation and Chemeotherapy in Pulmonary Metastates from Carcinoma of the Uterine Cervix and Endometrium," J. Nat'l Medical Assn., vol. 71, pp. 1061-1063.

Swinyard, E. A. (1980), "Introductin of New Drugs," Pharmaceutical Sciences, Mack Publishing Co., Easton, Pennsylvania, pp. 1365-1076.

Nikula et al. (1984). "Chromosome Aberrations in Lymphocytes of Nurses Handling Cystostatic Agents," Scand. J. Work Environ. Health, vol. 10, pp. 71-74.

U.S. Pharmacopoeia, "Doxorubicin Hydrochloride for Injection," 20th revision, p. 266.

U.S. Pharmacopoeia (1985), p. 119.

Formularium Der Nederlandse Apothekers, Band V (1983), p. I.8, I.24, I.63-1.64a, I.82, I.88.

Yoo (1977), Section "Injections" in the Korean Pharmacopoeia, pp. 3, 48-49.

Harris, D. C. (1995), Quantitative Chemical Analysis, Fourth Edition, W. H. Freeman & Company, New York, pp. 23ochloric Acid," S. Budavari, Ed., Merck & Co., Inc., Rahway, New Jersey, No. 4703, p. 756.

The Merck Index (1989), "Aclacinomycins," S. Budavari, Ed., Merck & Co., Inc., Rahway, New Jersey, No. 108, p.17.

Trissell, L. A. (1983), "Investigational Drugs," Handbook on Injectable Drugs, Third Edition, American Society of Hospital Pharmacists.

German Patent Office Decision dated October 8, 1996 revoking Patent No. 36 21844.

Harris, D. C. (1995), "Quantitative Chemical Analysis," 4th Edition, W. H. Freeman and Company. --

Item [56], **References Cited** , OTHER PUBLICATIONS; please insert the following references:

-- Bradner and Misiek, (1977) *The Journal of Antibiotics*, "Bohemic Acid Complex. Biological Characterization of the Antibiotics, Musettamycin and Marcellomycin," 30(6)519-522.

Kjeld Ilver, *Almen Galenisk Farmaci-Forelœsningsnoter*, Dansk Farmaceutforenings Forlag 1971, pp. 132-136. (English translation provided)

Gjelstrup et al. (1983), *Almen Farmaaci I*, Dansk Farmaceutforenings Forlag, Købonhavn, pp. 404-408, 440, 442-443, 447, 451. (English translation provided)

Erik Sandell, (1967), *Galenisk Farmaci*, 2nd edition, Stockholm, pp. 214. (English translation provided)

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,107,285
DATED : August 22, 2000
INVENTOR(S) : Gaetano Gatti et al

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Erk Sandell, (1982), *Galenisk Farmaci*, 3rd edition Stockholm, pp. 123. (English translation provided)

Svend Aage Schou & V. Gaunø Jensen (1959), *Troek af den flaeniske farmaci*, Store Nordiske Videnskabsboghandel, pp. 220. (English translation provided)

Arcamone, F. (1977), *Lloydia*, "New Antitumor Anthracyclines," 40(1):45-66.

Naff et al., (1982) *Anthracycline Antibiotics*, "Anthracyclines in the National Cancer Institute Program, Hassan S. El Khadam, editor, Academic Press, pp. 1-57.

Formularium Der Nederlandse Apothekers, (1983) pp..I.8, I.24, I.63.
Formularium DerNederlandse Apothekers, (1979) pp. I.64, I.82.
Formularium Der Nederlandse Apothekers, (1985) pp. I.64a.
Formularium Der Nederlandse Apothekers, (1989) pp. I.88.
Formularium Der Nederlandse Apothekers, (1992) pp. I.63a.

Harris, *Quantitative Chemical Analysis*, Fourth Edition, W.H. Freeman & Company, New York, pp. 240.

Bernard et al., editors (1969), *Rubidomycin A New Agent Against Cancer*, pp. ix-181.--;

Column 4,
Line 57, please delete "mg//$m^{2"}$ and insert -- mg/m^2 --;
Line 67, after "following" please insert -- experimental conditions: --;

Column 6,
Line 15, please delete "550° C" and insert -- 55° C --;

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,107,285
DATED : August 22, 2000
INVENTOR(S) : Gaetano Gatti et al

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

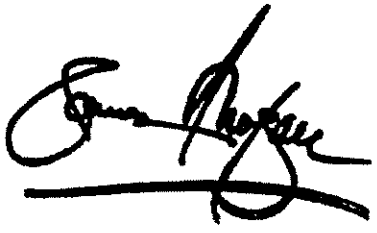
Column 9,
Line 59, please delete "Similarr" and insert -- Similar --;

Column 12,
Lines 21-23, please delete "The solution was filtered through a 0.22μ microporous membrane under nitrogen pressure. Volumes of 5 ml of the solution were distributed into type I colourless glass vials"; and

Column 24,
Line 9, Please delete "2.71 to 3.14" and insert -- 2.5 to 5.0 --.

Signed and Sealed this

Twenty-first Day of May, 2002



Attest:

Attesting Officer

JAMES E. ROGAN
Director of the United States Patent and Trademark Office

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,107,285
DATED : August 22, 2000
INVENTOR(S) : Gaetano Gatti et al.

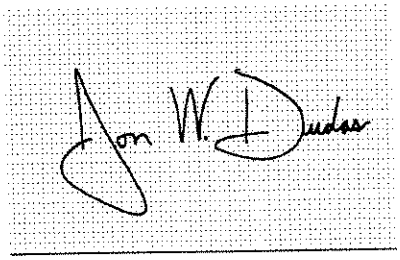
It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Title page,
Item [62], **Related U.S. Application Data**, after "Pat. No. 5,124,317" please insert -- , which is a division of application No. 07/385,999, filed on Jul. 27, 1989, now Pat. No. 4,946,831, which is a continuation of application No. 06/878,784, filed on Jun. 26, 1986, now abandoned --.

Column 1,
Line 6, after "U.S. Pat. No. 5,124,317" please insert -- , which is a division of application No. 07/385,999, filed on Jul. 27, 1989, now Pat. No. 4,946,831, which is a continuation of application No. 06/878,784, filed on Jun. 26, 1986, now abandoned --.

Signed and Sealed this

Eighteenth Day of May, 2004



JON W. DUDAS
Acting Director of the United States Patent and Trademark Office

EXHIBIT B

Neutral Citation Number: [2005] EWCA Civ 137

Case No: A3/2004/2433

IN THE SUPREME COURT OF JUDICATURE
COURT OF APPEAL (CIVIL DIVISION)
ON APPEAL FROM THE HIGH COURT OF JUSTICE
CHANCERY DIVISION (PATENTS COURT)
Mr Roger Wyand QC
HC-04-CO1628

Royal Courts of Justice
Strand, London, WC2A 2LL

Date: 17/02/2005

Before :

THE PRESIDENT
THE RT HON LORD JUSTICE JACOB
and
THE RT HON LORD JUSTICE HOOPER

Between :

(1) Mayne Pharma Pty Ltd **(2) Mayne Pharma plc**	**Respond-Ents/ Claimants**
- and - **Pharmacia Italia SPA**	**Appellant/ Defendant**

Richard Miller QC (instructed by Clifford Chance) for the Claimants
Colin Birss (instructed by Taylor Wessing) for the Defendant

Hearing date : 9 February 2005

Judgment Approved by the court for handing down (subject to editorial corrections)

Lord Justice Jacob:

1. This is a patentee's appeal in a case rightly subjected to the streamlined procedure. The litigation began on 17th May 2004 when the respondents ("Mayne") commenced proceedings for a declaration of non-infringement of Pharmacia's UK patent No. 2,178,311. A counterclaim for infringement followed. The only issue was whether Mayne's product falls within claim 1 of the Patent. The case was heard before Mr Roger Wyand QC, sitting as a Deputy Judge. He gave judgment, holding non-infringement, on 1st November 2004 and granted permission to appeal. So the case has gone from start to determination on appeal in less than 9 months.

What the dispute is about

2. Mayne wish to sell an injectable solution of an anti-cancer drug called epirubicin (an anthracycline glycoside) hydrochloride. They say it does not fall within any of the claims of the patent. Pharmacia say it does. It is agreed that the whole question turns on claim 1. This reads:

> "An injectable, ready-to-use, sterile, pyrogen-free, anthracycline glycoside solution which consists essentially of a physiologically acceptable salt of an anthracycline glycoside dissolved in a physiologically acceptable aqueous solvent therefor at an anthracycline glycoside concentration of from 0.1 to 50 mg/ml, which has not been reconstituted from a lyophilizate and the pH of which has been adjusted to from 2.5 to 5.0 solely with a physiologically acceptable acid, the said acid being selected from hydrochloric, sulfuric, phosphoric, acetic, succinic, tartaric, ascorbic, citric, glutamic, methanesulphonic or ethanesulphonic acid."

3. "Lyophilization" (US spelling) means freeze-drying. What Mayne do is described, it is agreed accurately, by the Deputy Judge as follows:

> "Mayne purchase epirubicin hydrochloride which has been subjected to a bulk lyophilization process. Mayne takes this lyophilizate, dissolve it in water, add [...]. The resulting solution is [...] and is then filled into vials [...]."

4. So lyophilization of the epirubicin hydrochloride forms part of the history of Mayne's product, but it is not the immediate precursor to its production – it is an "upstream" process. Is the final product nonetheless covered by the claim? This turns on its meaning, particularly the words *solution ... which has not been reconstituted from a lyophilizate.* It is conceded that the Mayne process fulfils the remainder of the claim, pH adjustment with appropriate acid.

The Principles of Construction

5. To decide upon that meaning one must construe the claim in context. I summarised the principles in paragraph 41 of my judgment in *Technip SA's Patent* [2004] RPC 919. The House of Lords in *Kirin-Amgen* [2004] UKHL 46, through Lord Hoffmann's speech, has approved those principles (save for one minor matter) and provided a much fuller justification for them than did I. As a practical working guide, it will generally be sufficient to use my summary as approved. I repeat it here, but stripped down to bare essentials:

> "(a) The first, overarching principle, is that contained in Art 69 itself.
>
> (b) Art 69 says that the extent of protection is determined *by the terms of the claims.* It goes on to say that the description and drawings shall be used to interpret the claims. In short the claims are to be construed in context.
>
> (c) It follows that the claims are to be construed purposively – the inventor's purpose being ascertained from the description and drawings.
>
> (d) It further follows that the claims must not be construed as if they stood alone – the drawings and description only being used to resolve any ambiguity. Purpose is vital to the construction of claims.
>
> (f) Nonetheless purpose is not the be-all and end-all. One is still at the end of the day concerned with the meaning of the language used. Hence the other extreme of the Protocol – a mere guideline – is also ruled out by Art 69 itself. It is the terms of the claims which delineate the patentee's territory.
>
> (g) It follows that if the patentee has included what is obviously a deliberate limitation in his claims, it must have a meaning. One cannot disregard obviously intentional elements.
>
> (h) It also follows that where a patentee has used a word or phrase which, acontextually, might have a particular meaning (narrow or wide) it does not necessarily have that meaning in context.
>
> (i) It further follows that there is no general "doctrine of equivalents".
>
> (j) On the other hand purposive construction can lead to the conclusion that a technically trivial or minor difference between an element of a claim and the corresponding element of the alleged infringement nonetheless falls within the meaning of the element when read purposively. This is not

because there is a doctrine of equivalents: it is because that is the fair way to read the claim in context.

(k) Finally purposive construction leads one to eschew what Lord Diplock in *Catnic* called (at p.243):

> "the kind of meticulous verbal analysis which lawyers are too often tempted by their training to indulge.""

The Skilled Man and Common General Knowledge

6. In this case it is agreed that the "Protocol questions" do not assist. What matters is the meaning of the claim read in context. Since the claim is assumed to be read by the person skilled in the art, it is sensible to begin by summarising his relevant background knowledge - the common general knowledge. I accept here, as Mr Birss, for Mayne, contended, that the relevant notional skilled man would be a pharmaceutical manufacturer, not merely a hospital pharmacist. Such a man (or team) would have knowledge not only of how the end product was to be used but also how to make it.

7. In particular he would know that:

i) The active ingredient to be used for the invention (anthracycline glycosides) were anti-tumour agents having widespread actual use;

ii) The agents were very toxic so that any risk of medical staff or manufacturing staff coming into accidental contact with them was serious;

iii) The existing products on the market were vials containing a "cake" consisting of a mixture of the active ingredient with an excipient such as lactose;

iv) The vials were used by injecting solvent through the rubber stopper to dissolve the cake. Shaking was necessary. Once the solid material had been dissolved there could be a bit of adjustment to get the solution toward isotonicity;

v) The cake within the vials consisted of a lyophilized product. They were made this way: the appropriate amount of a solution containing the active ingredient and the excipient or bulking agent was placed in the open vials. These were placed in lyophilizing conditions. Broadly (the details do not matter) this consisted of freezing followed by low pressure to evaporate the ice;

vi) The resulting product was, to use Mr Birss's word, "fluffy" – it had a low-bulk density. So there is more risk involved in handling this than handling crystalline material. The latter, being denser, is less apt to fly about;

vii) The reason for using the solid product in the vials, rather than simply having a solution was because solutions did not have very good stability – the product would deteriorate.

The specification of the patent

8. With that, I can turn to the specification. Its title is "Injectable ready-to-use solutions containing an antitumor anthracycline glycoside." The opening general words say this:

> "The present invention relates to a stable intravenously injectable ready-to-use solution of an antitumor anthracycline glycoside, e.g. doxorubicin, to a process for preparing such a solution, and provide the same in a sealed container, and to a method for treating tumors by the use of the said ready-to-use solution."

9. Next it acknowledges that the anthracycline glycoside compounds are well known and used as anti-tumor agents. It then sets out the nature of the existing products on the market:

> "At present, anthracycline glycoside antitumor drugs, in particular, e.g., doxorubicon, are solely available in the form of lyophilized preparations, which need to be reconstituted before administration."

10. After summarising two references which discuss the dangers to medical personnel from this type of agent in general, the patent says this:

> "To administer a lyophilized preparation, double handling of the drug is required, the lyophilized cake having to be first reconstituted and then administered and, moreover, in some cases, the complete dissolution of the powder may require prolonged shaking because of solubilization problems."

11. It then states the problem to be solved by the invention:

> "As the risks connected with the manufacturing and the reconstitution of a lyophilized preparate would be highly reduced if a ready-to-use solution of the drug were available, we have developed a stable, therapeutically acceptable intravenously injectable solution of an anthracycline glycoside drug, e.g. doxorubicin, whose preparation and administration does not require either lyophilization or reconstitution."

12. Next it sets out what the invention is in the so-called consistory clause. It is repeated in claim 1 so I need not set it out again. There then follows a second consistory clause, which corresponds to independent claim 31:

> "A process for producing a solution according to any one of the preceding claims; which process comprises dissolving the physiologically acceptable salt of the anthracycline glycoside, which salt is not in the form of a lyophilizate, in the physiologically acceptable aqueous solvent therefor; adding solely the physiologically acceptable acid to adjust the pH within the said range as desired; optionally, adding an additional component selected from a co-solublizing agent, a tonicity adjustment agent and a preservative to the solution; and then passing the resulting solution through a sterilising filter."

13. There then follows detail about how the solution is made. None of the detail matters for present purposes save this: that the description of the detailed variants of the process at no point mentions the use of lyophilized product. All the 12 examples start with the words "Doxorubicin.HCl was dissolved ..." without explicitly saying whether it was lyophilized or not.

14. The last passage I need mention is a general statement on p. 9 about an advantage of the invention:

> "With the solutions of the invention it is possible to obtain compositions having a very high concentration of the anthracycline glycoside active substance even at 50 mg/ml. This constitutes a great advantage over the presently available lyophilized preparates wherein high concentrations of anthracycline glycoside can only be obtained with difficulty because of solubilization problems encountered in reconstitution, mainly with saline. The presence of the excipient, e.g. lactose, in the lyophilized cake, and its generally high proportion in respect of the active substance, even up to 5 parts of excipient per part of active substance, has a negative effect on solubilization so that difficulties may arise in obtaining dissolution of the lyophilized cake, especially for concentrations of anthracycline glycoside higher than 2 mg/ml."

The detailed arguments on construction

15. Mr Richard Miller QC for the patentees contended that the patent was essentially about formulation of the ready-to-use solution. It was this formulation step which had not to involve lyophilization and its reconstitution on the ward. The starting

materials for the formulation were not part of the invention. He submitted in detail that:

i) The heart of the invention was, as its title said, an injectable ready-to-use solution.

ii) The passage about "the manufacturing and the reconstitution" is of "such preparations", i.e. the vials on the market. It is saying that the making and use of these each involves exposing people to risk. The workers at risk are those who operate the lyophilizing machines containing the vials. The medical workers at risk are those who have to inject solution into the vials to reconstitute (dissolve) the solid material within them.

iii) The passage about administration ("To administer a lyophilized preparation ..") is clearly only about the formulated product. The "lyophilized preparation" is that contained in such a product.

iv) The passage about "The risks connected with the manufacturing and the reconstitution of a lyophilized preparate ..." is likewise about the final product. What it is saying is that if final product were a ready-to-use stable solution the risks would be reduced. The risks being talked about are those concerned with the manufacture of the vials containing lyophilized preparations and their use.

v) The passage on p. 9 about the great advantage of the invention is by comparison with the "presently available lyophilized preparates" i.e. those on the market now. It is saying you can get high concentration of the active ingredient and avoid the solubilisation problems of the prior art. That has nothing to do with the nature of the original raw material active ingredient.

vi) So the essential teaching of the patent is not concerned with the nature of that basic raw material. It is about how you make a stable, ready-to-use solution from such a material.

vii) The fact that claim 31 is more limited than claim 1 (as it is) makes no difference. Claim 31 is, Mr Miller accepts, not infringed. This is because it is specifically limited to a process which starts with a raw material ("salt") which "is not in the form of a lyophilizate". Mr Miller says that by contrast in claim 1 it is "the solution which has not been reconstituted from a lyophilizate". There is a shift from the unlyophilized starting material of claim 31 to the unlyophilized material used to make the ready-to-use solution.

16. Mr Birss submits that his case is crucially dependent upon whether the Deputy Judge was right in his paragraph 36:

> "36. On a fair reading of the claims and in the context of the specification and such evidence of common general knowledge as is before me I find that the skilled addressee would form the view that the patentee regarded lyophilization as not just an unnecessary but as an undesirable process step in the production of the injectable solution and intended to exclude a solution made by the use of such a step, even if it were to be followed by other steps, such as the adjustment of pH and sterilising by filtration."

17. Putting it another way, he submitted that the whole teaching of the patent is about the complete avoidance of lyophilization. You do not need lyophilization at any stage. And it is that which is to be avoided if you are to avoid danger to workers during any part of the manufacture. As he put it "you can throw away the lyophilizing machine."

18. He drew a homely analogy – with instant coffee. If you want a cup of real coffee (i.e. coffee which has not been reconstituted from a lyophilizate) containing milk and sugar you will not be satisfied with a cup of instant coffee where the milk and sugar has been added after the reconstitution.

19. Mr Birss further relied upon the process aspect of the invention – claim 31. First he pointed out that if the examples were truly indifferent as to whether the starting material was lyophilized or not, then none of them would be examples of the process of the invention. So it was implicit that the starting material was not lyophilized. Second he submitted that claim 31 tracks claim 1 and in particular both claims use the word "lyophilizate". If Mr Miller were right then the word would have a different meaning in each claim which was improbable.

The Deputy Judge's conclusions

20. I have already quoted the most crucial paragraph of his judgment. But I should mention some other points too. First there is the way he dealt with claim 31. He said this:

> "28. Pharmacia counters by saying that claim 31 is effectively dependent on claim 1 and is therefore narrower than claim 1 and should be construed in such a way. This is not strictly correct. Claim 31 is a process claim whereas claim 1 is a product claim. Whilst it is correct that the process of claim 31 may not be the only process that will produce a product within claim 1 this does not mean that it must necessarily be construed as a subset of the processes that can produce such a product. There may be other processes: there may not. It is neutral."

21. I think that is right. In general in a patent with product and process claims one may perhaps expect the process to produce the product, but there is no necessary corollary that the product must be made only by the process. All depends on the language used in context.

22. In the preceding paragraph the Judge said this:

> "27. Mayne submit that their product is made by the process of claim 31 except that the salt of the anthracycline glycoside which they dissolve **is** in the form of a lyophilizate. Thus, they do not infringe claim 31, as is acknowledged by Pharmacia. They point out that the examples being silent as to how the API is produced, it must be assumed that the API is not a lyophilizate otherwise there is no example of the process claimed. Thus, they say, the skilled addressee would understand the phrase in claim 1 "which has not been reconstituted from a lyophilizate" as excluding a solution which has been made by the process of claim 31 but with the starting material, the API, being a lyophilizate."

23. Mr Birss submitted that the Judge's comment about the claim 31 argument being "neutral" did not apply to this paragraph. I think he is right. On the other hand the Judge here does no more than record Mr Birss' argument about the examples. He never found it necessary to take the argument specifically into account, though he may have done in his crucial paragraph 36.

24. Next I should mention the Judge's paragraphs 33 and 34:

> "I have two problems with Pharmacia's approach to construction of the disputed phrase. The first is that even if the patent does not teach achieving stability by adjusting the pH the claim also refers to an anthracycline glycoside concentration of from 0.1 to 50 mg/ml. The passage set out above from page 9 line 11 of the patent explains that this is an advantage over "the presently available lyophilized preparates". I have heard no evidence as to how the skilled addressee would regard this passage but on its face it seems to be teaching away from the use of lyophilizates.
>
> The second problem is more fundamental. If one concludes that the skilled addressee does not regard the disputed phrase as necessarily excluding **any** lyophilization/reconstitution step, where does he/she draw the line? The suggestion by Pharmacia is that the skilled addressee would understand the phrase to mean that lyophilization was not used on the final product but could have been used on a precursor. This, says Pharmacia, would only exclude precisely what was done before in the hospital pharmacy."

25. I do not agree with either of these points. As Mr Miller pointed out the passage on p.9 is by way of contrast with the existing product – "the teaching away from lyophilizates" relates only to lyophilizates in the final product.

26. Nor do I see any real problem about where the line is drawn. Mr Miller put it this way: "only if the step of reconstitution produces a ready-to-use solution is there no infringement." Mr Birss suggested there was a problem here: suppose you reconstituted and then diluted the solution or added saline for isotonicity – as you sometimes did with the prior art. Would that mean no infringement? I see no problem. The product is either ready-to-use or it is not. If it is, then if the immediately prior step was reconstitution, there is no infringement – otherwise there is.

27. Finally the Judge thought there was support from a linguistic analysis of the claim. I do not go into the detail of this – Mr Birss did not seek to support it as such. His support for the Judge, as I have already said, rested essentially on paragraph 36.

My opinion

28. I have come to the conclusion that Mr Miller is right, essentially for the reasons he advanced. I need elaborate only a little. I think the skilled man would see the real point of the teaching in the description as being the provision of a stable, ready-to-use solution. Such a desirable substance was not previously available. The patent teaches him how to make it. He can make it without having to lyophilize the material in the vials. He knows he will have to start his formulation with active ingredient raw material. But he would not regard the nature of that as part of the formulation process. The patent teaches him how to do away with a previously essential lyophilization.

29. When he comes to read claim 1, knowing that its purpose in law is to set out the monopoly, he sees that it is the "ready-to-use solution" which must not "have been reconstituted from a lyophilizate." With the understanding of the purpose and teaching of the description he would read it as meaning that the solution itself has not been made by reconstitution – it is avoidance of that which fulfils the purpose of doing away with the previously essential step. If he considered the nature of the starting raw material, lyophilized or not, he would see it made no real difference – just that starting with lyophilizate would introduce an unnecessary complication.

30. I think this construction is that which is consistent with the inventor's purpose as disclosed in his specification – the manufacture of a ready-to-use solution which does not involve the previously essential lyophilization stage.

31. As to Mr Birss's coffee example, like many analogies it is beguilingly misleading – there is no true analogy because coffee in its raw material form can never be lyophilized. Nor do I think it matters whether the examples are read as starting with

unlyophilized material – whether they do or not is not what matters because they are essentially about producing the stable solution.

32. Accordingly I would allow the appeal. I would not want to part from this case without paying tribute to the high quality of the argument on both sides. Sadly, however, I must also record the fact that I was most disappointed to see the quite extraordinary number of files of paper produced, quite unnecessarily, for this appeal. We were only referred to two pages not included in the one main file. They were obviously not wanted on voyage or to put it more formally not "relevant to proceedings in the Court of Appeal" within the meaning of para. 15.1(1) of the Practice Direction to Part 52 of the CPR. No doubt this will be taken into account on assessment of costs.

Lord Justice Hooper:

33. I agree.

Dame Elizabeth Butler-Sloss P:

34. I also agree.

EXHIBIT C

FEDERAL COURT OF AUSTRALIA

Pharmacia Italia S.P.A v Mayne Pharma Pty Ltd [2005] FCA 1066

INTELLECTUAL PROPERTY – patents – claim for infringement – clarity of expression used in a claim – exclusionary integer – principles of construction – whether permissible to qualify a claim by reference to the body of specification – whether substance of invention taken.

Patents Act 1990 (Cth), ss 40(2)(b), 117, 120

Assidoman Multipack (formerly Multipack Wraparound Systems) v Mead Corporation [1995] RPC 321 cited
Attorney-General v Prince Ernest Augustus of Hanover [1957] AC 436 cited
Catnic Components Ltd v Hill & Smith Ltd (No. 1) [1982] RPC 183 discussed
Clark v Adie (1875) LR 10 Ch. App. 667 cited
Commonwealth Industrial Gases Ltd v MWA Holdings Pty Ltd (1990) 180 CLR 160 followed
Décor Corporation Pty Ltd v Dart Industries Inc (1998) 13 IPR 385 applied
Electric & Musical Industries Ltd v Lissen Pty Ltd (1936) 54 RPC 23 cited
Flexible Steel Lacing Co v Beltreco Ltd (2000) 49 IPR 331 cited
General Tire & Rubber Co. v Firestone Tyre & Rubber Co Ltd (No. 1) [1972] RPC 457 cited
Improver Corp v Remington Consumer Products Ltd [1990] FSR 181 cited
Interlego AG v Toltoys Pty Ltd (1973) 130 CLR 461 cited
Kimberly-Clark Australia Pty Limited v Arico Trading International Pty Limited and Others (2001) 207 CLR 1 applied
Kirin-Amgen Inc v Hoescht Marion Roussel Ltd [2005] 1 All ER 667 cited
Leonardis v Sartas No. 1 Pty Ltd (1996) 67 FCR 126 cited
Marconi v Mullard (1923) 40 RPC 159 cited
Martin Engineering Co v Trison Holdings Pty Ltd (1989) 14 IPR 330 cited
Mayne Pharma Pty Ltd and Mayne Pharma plc v Pharmacia Italia SPA [2005] EWCA Civ 137 considered
Minerals Separation North American Corp v Noranda Mines (1952) 69 RPC 81 cited
Minnesota Mining and Manufacturing Co v Beiersdorf (Australia) Ltd [1979-1980] 144 CLR 253 cited
Nesbit Evans Group Australia Pty Ltd v Impro Ltd and Anor (1997) 39 IPR 56 cited
Nicaro Holdings Pty Ltd v Martin Engineering Co (1990) 91 ALR 513 cited
Olin Corporation v Super Cartridge Co Pty Ltd and Anor (1977) 51 ALJR 525 applied
Populin v H.B. Nominees Pty Ltd (1982) 41 ALR 471 applied
Radiation Ltd v Galliers & Klaerr Pty Ltd (1938) 60 CLR 36 applied
Rehm Pty Ltd v Websters Security Systems (International) Pty Ltd and Ors (1988) 81 ALR 79 cited
Root Quality Pty Ltd and Anor v Root Control Technologies Pty Ltd and Others (2000) 177 ALR 231 cited
Walker v Alemite Corp (1933) 49 CLR 643 applied
Welch Perrin and Company Proprietary Limited v Worrel (1961-1962) 106 CLR 588 followed

GS Banker and CT Rhodes, *Modern Pharmaceutics* (1979)
Dictionary of Pharmacy, Pharmaceutical Products Press, 2004

PHARMACIA ITALIA S.P.A and PFIZER (PERTH) PTY LIMITED v MAYNE PHARMA PTY LTD and F H FAULDING & CO LTD and FAULDING HEALTHCARE PTY LTD

VID 439 OF 2003

CRENNAN J
5 AUGUST 2005
MELBOURNE

GENERAL DISTRIBUTION

IN THE FEDERAL COURT OF AUSTRALIA
VICTORIA DISTRICT REGISTRY **V439 OF 2003**

BETWEEN:	**PHARMACIA ITALIA S.P.A** **FIRST APPLICANT**
	PFIZER (PERTH) PTY LIMITED **SECOND APPLICANT**
AND:	**MAYNE PHARMA PTY LTD** **FIRST RESPONDENT**
	F H FAULDING & CO LTD **SECOND RESPONDENT**
	FAULDING HEALTHCARE PTY LTD **THIRD RESPONDENT**

JUDGE:	**CRENNAN J**
DATE OF ORDER:	**5 AUGUST 2005**
WHERE MADE:	**MELBOURNE**

THE COURT ORDERS THAT:

1. The parties to prepare short minutes of final orders on liability in accordance with these reasons and include any other orders or directions as appropriate for the further disposition of the matter.

Note: Settlement and entry of orders is dealt with in Order 36 of the Federal Court Rules.

GENERAL DISTRIBUTION

IN THE FEDERAL COURT OF AUSTRALIA
VICTORIA DISTRICT REGISTRY **V439 OF 2003**

BETWEEN:	**PHARMACIA ITALIA S.P.A** **FIRST APPLICANT**
	PFIZER (PERTH) PTY LIMITED **SECOND APPLICANT**
AND:	**MAYNE PHARMA PTY LTD** **FIRST RESPONDENT**
	F H FAULDING & CO LTD **SECOND RESPONDENT**
	FAULDING HEALTHCARE PTY LTD **THIRD RESPONDENT**
JUDGE:	**CRENNAN J**
DATE:	**5 AUGUST 205**
PLACE:	**MELBOURNE**

REASONS FOR JUDGMENT

INTRODUCTION

1 This proceeding concerns the alleged infringement of Australian Patent No. 598197, entitled 'Injectable ready-to-use solutions containing an antitumor anthracycline glycoside' ('Patent') within s 117 of the *Patents Act 1990* (Cth) (the '*Patents Act*'). The first applicant, Pharmacia Italia S.p.A, a company incorporated in Italy, is the registered proprietor of the Patent; the second applicant, Pfizer (Perth) Pty Limited, a company incorporated in Australia, is a manufacturer of pharmaceuticals (together, 'the applicants'). Since 23 July 2003 the second applicant has been the exclusive licensee in Australia of the invention described in the Patent in relation to epirubicin hydrochloride.

2 The first respondent, Mayne Pharma Pty Ltd is a manufacturer, distributor and exporter of pharmaceutical products. The second and third respondents are F H Faulding & Co Ltd, and Faulding Healthcare Pty Ltd respectively. The three respondent companies form

part of the Mayne Pharma group of companies, all of which are incorporated in Australia (together, 'the respondents'). The applicants allege that the respondents have infringed certain claims of the Patent by 'manufacturing, selling, using and keeping a ready –to-use antitumor anthracycline glycoside solution as claimed in the Patent' (the 'respondents' product') and have made application to this court under s 120 of the *Patents Act*.

3 It is noted that on 23 July 2003 an order by consent was made in the following terms:

> *'The decisions of the questions of law and issues of fact in respect of the validity (if put in issue by way of Cross-claim) and liability for infringement of Australian Letters Patent 598197 be made separately from and before any other question in the proceeding.'*

Accordingly, the only question to be resolved by the Court, at this stage, is whether the respondents have infringed certain claims of the Patent by making and selling epirubicin hydrochloride in injectable ready-to-use solutions.

4 The primary issue of infringement is whether the respondents' product has been 'reconstituted from a lyophilizate' as that phrase is used in Claim 1 of the Patent, which states that the invented pharmaceutical product 'has not been reconstituted from a lyophilizate'. A secondary issue is whether the specific occasions on which the respondents used sodium hydroxide, in addition to hydrochloric acid, to adjust the pH of the solution avoid infringement, when Claim 1 of the Patent refers to the pH being adjusted '**solely** with a physiologically acceptable acid' (emphasis added).

5 The invention, the subject of the Patent relates to:

(a) a pharmaceutical product, being a stable intravenously injectable ready-to-use solution of an antitumor anthracycline glycoside, e.g. doxorubicin;

(b) a process for preparing such a solution, [providing] the same in a sealed container; and

(c) a method for treating tumours by the use of the ready-to-use solution.

6 The priority date of the Patent is 2 August 1985. Anthracycline glycosides are anticancer drugs which were well known at the priority date. It appears that at that time they were commercially available solely in the form of lyophilized preparations (in a solid form) that needed to be reconstituted into an injectable form (a liquid) before administration to a patient.

7 Lyophilization is a process which is colloquially described as 'freeze-drying' whereby the temperature of the subject material is lowered to freeze it. A vacuum is drawn then the temperature is raised such that the frozen solvent (usually water) sublimates directly from a solid to a gas. Accordingly, a 'lyophilizate' is the dried or solid form of a product which was formerly in a liquid form and has undergone lyophilization.

8 Anthracycline glycosides cannot be administered to a patient in their lyophilized solid form yet they are unstable in aqueous solution and degrade, resulting in both a loss of pharmaceutical activity and the precipitation of solid particles, which prevents them from being administered intravenously. Because of the problems related to instability, anthracycline glycosides were not manufactured in the form of ready-to-use solutions before the priority date. As mentioned above, they were only marketed in the form of a lyophilized solid in a vial, which was required to be reconstituted into a liquid form before the product could be injected into a patient.

9 In the body of the Patent specification it is noted that the manufacturing and reconstitution of such preparations expose the personnel involved to risks of contamination which are particularly serious because of the toxicity of the antitumour substances. The complete specification states:

> *'To administer a lyophilized preparation, double-handling of the drug is required, the lyophilized cake having to be first reconstituted and then administered and, moreover, in some cases, the complete dissolution of the powder may require prolonged shaking because of solubilization problems.'* (p2)

10 The complete specification indicates that the invention is targeted at circumventing the problems of handling cytotoxic material safely:

> *'As the risks connected with the manufacturing and the reconstitution of a lyophilized preparate would be highly reduced if a ready-to-use solution of the drug were available, we have developed a stable, therapeutically acceptable intravenously injectable solution of an anthracycline glycoside drug, e.g. doxorubicin, whose preparation and administration does not require either lyophilization or reconstitution.'* (p2)

THE COMPLETE PATENT SPECIFICATION

11 The entitlement of the complete specification is set out in paragraph 1 above. The body of the Patent specification describes the product, process and method of treatment

which are defined in the claims thus:

> *'The present invention relates to a stable intravenously injectable ready-to-use solution of an antitumour anthracycline glycoside, e.g. doxorubicin, to a process for preparing such a solution, and provide the same in a sealed container, and to a method for treating tumours by the use of the said ready-to-use solution.'*

12 Then follows a description of relevant prior art and the problems which the invention seeks to overcome as set out in paragraphs 9 and 10 above.

13 The complete specification then sets out the consistory clause for the product, which underlines Claim 1, as follows:

> *'According to the present invention, there is provided a sterile, pyrogen-free, anthracycline glycoside solution which comprise a physiologically acceptable salt of an anthracycline glycoside dissolved in a physiologically acceptable aqueous solvent therefor at an anthracycline glycoside concentration of from 0.1 to 50 mg/ml, which has not been reconstituted from a lyophilizate, and the pH of which has been adjusted from 2.5 to 5.0 solely with a physiologically acceptable acid. Preferably the solution of the invention is provided in a sealed container.'*

14 The language of the consistory clause for the product is then reflected in a preferred embodiment as follows:

> *'According to a particularly preferred embodiment of the invention, there is provided a sterile, pryogen-free, doxorubicin solution which consists essentially of a physiologically acceptable salt of doxorubicin dissolved in a physiologically acceptable solvent therefor at a doxorubicin concentration of from 0.1 to 50 mg/ml, which has not been reconstituted from a lyophilizate and the pH of which has been adjusted from 2.5 to 5.0 solely with a physiologically acceptable acid.'*

15 The complete specification then sets out the consistory clause for the process as follows:

> *'The invention also provides a process for producing a sterile, pyrogen-free anthracycline glycoside solution with a pH of from 2.5 to 5.0, which process comprises dissolving the physiologically acceptable salt of the anthracycline glycoside, which salt is not in the form of a lyophilizate, in the physiologically acceptable solvent therefor; adding solely a physiologically acceptable acid to adjust the pH within the said range as desired; passing the resulting solution through a sterilising filter and, optionally, adding an additional component selected from a co-solubilizing agent, a tonicity adjustment agent and a preservative, for instance of the kind previously specified, to the solution prior to passing the solution through the sterilising filter.'*

16 The complete specification then proceeds:

> *'With the solutions of the invention it is possible to obtain compositions having a very high concentration of the anthracycline glycoside active substance even at 50 mg/ml and more. This constitutes a great advantage over the presently available lyophilized preparates wherein high concentrations of anthracycline glycoside can only be obtained with difficulty because of solubilization problems encountered in reconstitution, mainly with saline. The presence of the excipient, e.g. lactose in the lyophilized cake, and its generally high proportion in respect of the active substance, even up to 5 parts of excipient per part of active substance, has a negative effect on solubilization so that difficulties may arise in obtaining dissolution of the lyophilized cake.'*

17 Then the complete specification sets out the consistory clause for the method as follows:

> *'... according to the invention there is also provided a method of inhibiting the growth of a tumour, in particular one of those indicated above, which comprises administering to a host suffering from said tumour an injectable solution according to the invention containing the active drug substance in an amount sufficient to inhibit the growth of said tumour. The injectable solutions of the invention are administered by rapid intravenous injection or infusion according to a variety of possible dose schedules.'*

18 Further, in terms of preferred embodiments, the complete specification then provides 12 examples which 'illustrate but do not limit in any way the invention' and they include the dissolution of doxorubicin, and the adjustment of the solution's pH, followed by the filtration and containment of the solution in sealed vials. The stability of the 12 solutions is then described over various periods of time.

19 The invention is the subject of 26 claims. The pharmaceutical product (solution) claims are claims 1 to 19 and 22. The process claims are claims 20, 21, 23 and 24 and the claims relating to a method of treatment using the product are claims 25 and 26.

20 The applicants allege the respondents have infringed:

(a) product claims 1 to 3, 5 to 10, 14 and 15; and

(b) method claims 25 and 26.

21 Claim 1 is the only independent claim relating to a solution of the invention and the only claim that refers to the invention as a solution 'which has not been reconstituted from a

lyophilizate' and 'the pH of which has been adjusted from 2.5 to 5.0 solely with a physiologically acceptable acid.'

22 The parties are agreed that resolution of the construction of Claim 1, in respect of those parts emphasised below, will resolve the controversy between them. Claim 1 is now set out with numbers (1) to (6) interpolated to identify its six integers:

> *'1. (1) A sterile,*
> *(2) pyrogen-free*
> *(3) anthracycline glycoside solution*
> *(4) which comprises*
> *(i) a physiologically acceptable salt of an anthracycline glycoside*
> *(ii) dissolved*
> *(a) in a physiologically acceptable aqueous solvent therefor*
> *(b) at an anthracycline glycoside concentration of from 0.1 to 50 mg/ml,*
> *(5) **which has not been reconstituted from a lyophilizate***
> *(6) and the pH of which*
> *(i) has been adjusted from 2.5 to 5.0*
> *(ii) **solely** with a physiologically acceptable acid.'*

23 It is also necessary to set out Claim 20, the process claim, relied on by the respondents as an aid to construing Claim 1:

> *'20. A process for producing a sterile, pyrogen-free, anthracycline glycoside solution with a pH of from 2.5 to 5.0, according to any one of the preceding claims; which process comprises dissolving a physiologically acceptable salt of the anthracycline glycoside, which salt is not in the form of a lyophilizate, in a physiologically acceptable aqueous solvent therefore; adding solely a physiologically acceptable acid to adjust the pH within the said range as desired; passing the resulting solution through a sterilising filter; and, optionally, adding an additional component selected from a cosolubilizing agent, a tonicity adjustment agent and a preservative to the solution prior to passing the solution through the sterilising filter.'*

24 The invention is for a new combination. Accordingly, to establish infringement, the applicants must demonstrate that the respondents have taken 'each and every one of the essential integers': *Populin v H.B. Nominees Pty Ltd* (1982) 41 ALR 471 at 475. The respondents have admitted their product has the features of the new combination in Claim 1

except those covered by integer (5) and the emphasised part of integer (6)(ii).

25 Each of the respondents is involved in one of the manufacture, distribution or sale of the respondents' product. In a written outline of submissions, the respondents' product is described as:

> *'. . . a sterile, pyrogen-free anthracycline glycoside solution which comprises a physiologically acceptable salt of an anthracycline glycoside dissolved in a physiologically acceptable aqueous solvent therefor at an anthracycline glycoside concentration of from 0.1 to 50 mg/ml. The pH of the solution has been adjusted to a figure within the range of 2.5 to 5.0.'*

26 The respondents assert that their product does not infringe the Patent because, at an early stage in the manufacturing process, the dissolution of bulk lyophilizate takes plaee, and that therefore their solution has been 'reconstituted from a lyophilizate', a feature of production which it asserts is expressly excluded by Claim 1 of the Patent. It can be noted in this context that the applicant conceded that the bulk powder used in the manufacture of the respondents' product is a lyophilizate.

27 The applicants assert that the Patent is to be construed such that the words 'which has not been reconstituted from a lyophilizate' in Claim 1 are limited to mean the process that takes place just prior to administration of the solution to a patient. They submit that the expression means (and thereby excludes from the monopoly claimed) solutions made up shortly before administration to a patient, which were known at the priority date and does not mean the dissolution of the lyophilizate in the respondents' method of manufacture. Therefore, it is submitted, the respondents' product is within the scope of Claim 1.

28 Thus the two questions to be resolved by the court are whether (i) the respondents' product has been 'reconstructed from a lyophilizate' as the phrase is used in Claim 1 and (ii) the pH of the respondents' product has been adjusted solely with a physiologically acceptable acid.

29 The claims in a complete specification define the invention: s 40(2)(b) of the *Patents Act*. They mark out the monopoly operating to disclaim what is not specifically and definitely claimed: *Walker v Alemite Corp* (1933) 49 CLR 643 at 656. This is to ensure that the public and specifically a manufacturer will not have difficulty being satisfied that a claim is not infringed: *General Tire & Rubber Co. v Firestone Tyre & Rubber Co Ltd (No. 1)*

[1972] RPC 457 at 515 (*'General Tire & Rubber Co.'*). There are no special rules for the interpretation of patent specifications: *Décor Corporation Pty Ltd v Dart Industries Inc* (1998) 13 IPR 385 at 391 (per Lockhart J) (*'Décor'*). The approach to be taken is discussed by the High Court in *Kimberly-Clark Australia Pty Limited v Arico Trading International Pty Limited and Others* (2001) 207 CLR 1 at [24] (*'Kimberly-Clark'*):

> *'It is well settled that the complete specification is not to be read in the abstract; here it is to be construed in the light of the common general knowledge and the art before 2 July 1984, the priority date; the court is to place itself "in the position of some person acquainted with the surrounding circumstances as to the state of [the] art and manufacture at the time".'*

30 The parties were substantially in agreement that the skilled addressee for the purposes of this case was a 'team' as is appropriate with highly developed technology: *General Tire & Rubber Co.* at 485. The team included not only a pharmacist working in a hospital but also persons involved in the manufacture of cytotoxic drugs for hospital pharmacists, as at the priority date 2 April 1985.

31 Speaking broadly, it was contended for the applicants that the word 'reconstituted' as it occurs in the phrase 'has not been reconstituted from a lyophilizate' in Claim 1 was a term of art. It was conceded that the word had an ordinary English meaning in pharmaceutical science but it was contended that it also had a specialist meaning in pharmaceutical science. Thus the word 'reconstitution' was capable of having more than one meaning. It was submitted that ambiguity or lack of clarity could be dispelled by resort to the body of the specification.

32 Alternatively, if 'reconstituted' as used in Claim 1 is not a term of art, it was contended that the complete specification, ie. the context showed the expression was used in a special and narrow sense. Either way the exclusionary integer would indicate to the skilled addressee that the invention did not cover known prior art.

33 It was contended for the respondents that the word 'reconstituted' as used in Claim 1 is not a term of art. Next, it was submitted it was a word of ordinary English meaning, which as a matter of principle precluded resort to the body of the specification to qualify Claim 1. Further, the express terms of Claim 1 were relied on as not limiting the phrase in contention, to solutions in a vial or to injectable solutions. It was submitted that the applicants' attempts to construe the exclusionary integer narrowly should fail.

34 Numerous experts gave evidence about the meaning of the term 'reconstituted' which is unexceptional given the terms of the dispute: *Minnesota Mining and Manufacturing Co v Beiersdorf (Australia) Ltd* [1979-1980] 144 CLR 253 at 270 ('*Minnesota Mining*'); *Leonardis v Sartas No. 1 Pty Ltd* (1996) 35 IPR 23 at 36.

35 The applicants' experts did not dispute the fact that 'reconstitution' has a usual, or as they put it, general meaning, perhaps best exemplified by the relevant entry in the 1982 *Supplement to the Oxford English Dictionary*:

> *'**reconstituted**, that has been constituted or formed anew; applied spec. to food which has been dehydrated and subsequently made ready for use by adding liquid.'*

36 It was also conceded by the applicants that the word 'reconstituted' was used in the pharmaceutical sciences with a usual but narrower meaning of describing the step of putting lyophilized material into solution. This is exemplified in an entry after the priority date in the *Dictionary of Pharmacy, Pharmaceutical Products Press, 2004*:

> *'**reconstitution** process of adding a solvent or suspending liquid (usually purified water) to a previously prepared spray-dried or freeze-dried drug formulation intended to be used in a short period of time (usually within two weeks) after the addition (generally refrigerated following reconstitution); example: reconstitution of an antibiotic suspension'*

37 Professor Stella, an American Professor of Pharmaceutical Chemistry, gave evidence on behalf of the applicants that as at the priority date, in 1985, all anthracycline glycosides were supplied for use as lyophilizates prepared in a particular way to produce an intravenously injectable solution.

38 Dr Williams, a specialist pharmacist in manufacturing from Westmead Teaching Hospital in New South Wales, gave evidence on behalf of the applicants of his experience also as at the relevant date. He gave evidence that anthracycline glycosides were provided to pharmacists in single dose sealed vials:

> *'. . . which had to be prepared by the pharmacist for administration to the patient by a reconstitution. A reconstitution was carried out as part of the general dispensing process in response to receipt of a prescription. The doses were reconstituted immediately prior to the administration to a patient, either on the day of administration or no more than one day before administration.'*

He also gave evidence he performed many such reconstitutions and trained many others in the procedure:

> *'Pharmacists used the term "reconstitution" to describe the act of adding a sterile diluent to a sterile solid drug in a vial (or, rarely, in an ampoule) to dissolve or suspend the drug in order to prepare an injection, installation or irrigation, and a product which is reconstituted has been prepared in this way.*
>
> *In the specific context of reconstituting cytotoxic drugs for intravenous injection, other important aspects of a reconstitution include the fact the resulting product must be fully dissolved and that the reconstituted solution must be free of pyrogens.*
>
> *Reconstitution technique is an important element of pharmacy training and practice. Hospital pharmacists, in particular, may perform reconstitutions many times a day; larger hospitals including Westmead have dedicated reconstitution units including cytotoxic reconstitution units, as I have mentioned. Accordingly, reconstitution is a well known procedure and the term "reconstituted" is well understood by pharmacists.'*

He did not accept that 'reconstitution' was a synonym for 'dissolution' in the context of hospital pharmacy practice.

39 The applicants also relied on the evidence of Dr Marshall, a Consulting Pharmaceutical Scientist from South Australia who gave the following evidence:

> *'I have been asked . . . to consider what term or expression would be used by pharmaceutical formulation chemists to describe the step where a lyophilizate is put into solution as part of a manufacturing process. The words I would use are "dissolve" or "dissolution". The words "dissolve" and "dissolution" are in my experience frequently used both orally and in writing (such as in operating manuals or manufacturing instructions) in describing processes involving putting solid pharmaceutical compounds into solution. I cannot recall (before or after 1985) seeing the words "reconstitute" or "reconstitution" used in a technical document (of which I have seen hundreds) relating to the process of dissolving pharmaceutical compounds in the manufacturing of pharmaceuticals or formulations of such pharmaceuticals.*
>
> *The word "reconstitution" is, however, used in the pharmaceutical industry in relation to finished product powders, whether lyophilized or not, which are dissolved or suspended before administration to a patient . . .'*

40 Dr Marshall referred to the text *Modern Pharmaceutics* by Gilbert S. Banker and Christopher T. Rhodes (1979) which states:

> *'Several ophthalmic drugs are prepared as sterile powders for reconstitution*

> *by the pharmacist before dispensing to the patient... The sterile powder is usually manufactured by lyophilization and is packaged separately from the diluent, and a sterile dropper assembly is provided. In powder form these drugs have a much longer shelf life than that of their solution forms. The pharmacist should use only the diluent provided with the product since it has been developed to maintain the optimum potency and preservation of the reconstituted solution. The pharmacists should use great care in performing the reconstitution to prevent microbial contamination of the sterile product and dropper. Each product has an expiration date for the reconstituted solution which should be explained to the patient along with the proper storage conditions and method of usage.'*

41 Professor Peter Stewart, Head of the Department of Pharmaceutics, Victorian College of Pharmacy, upon whom the applicants also rely, echoed the evidence of Dr Marshall as follows:

> *'Reconstitution has a particular meaning in the context of pharmacy. It refers to the following fundamental steps taken shortly before administration of the drug to the patient.*
>
> *(a) Taking a solid form of an active pharmaceutical compound (plus any excipients).*
>
> *(b) Adding a solvent to the solid to make an acceptable delivery system.*
>
> *The delivery system produced by reconstitution is referred to as "reconstituted".'*

Dr Stewart also gave evidence that:

> *'For injectable delivery systems reconstitution is usually a matter of hours before administration.'*

42 Dr Richard Oppenheim, a chemist with some 30 years experience in the area of 'human pharmaceuticals', was at the relevant time a member of the Pharmaceutics faculty of the Victorian College of Pharmacy in Melbourne. He gave clear evidence on behalf of the respondents that:

> *'The term* "reconstitution" *refers to the process of adding a suitable and appropriate liquid or liquid system to a solid that has previously been associated with that liquid or some other liquid system, to form a solution, dispersion or suspension suitable for its intended use. If a solid has undergone the process of reconstitution by the addition of a suitable liquid or liquid system, the resultant solution, dispersion or suspension is said to have been* "reconstituted".'

He also gave evidence of an instance of doxorubicin being available as bulk lyophilizate for research purposes only, as at the priority date. In this respect, his knowledge and experience differed from that of the other experts.

43 Dr Kenneth Brown, Consultant Pharmaceutical Scientist in Pharmaceutics, from New South Wales, provided a similar assessment as follows:

> *'The process of reconstitution does not necessarily involve bringing the solution back to exactly the same form as the previous solution. The practical essence of reconstitution is the re-association of the lyophilizate with solvent.*
>
> *In the pharmaceutical sciences* "reconstitution" *includes the reconstitution of a lyophilized product by a pharmacist immediately prior to administration. However, this is not the only meaning of the term.* "Reconstitution" *is a broad and non-specific term which applies at any time a lyophilizate is redissolved into a solvent or passes into solution.'*

44 The respondents' experts did not disagree that 'reconstitution' has a meaning, in the pharmaceutical sciences, of 'reconstitution of a lyophilized product prior to administration to a patient'. However, they did not accept that reconstitution in that pharmacy context can only occur shortly before administration to a patient. When cross-examined about the references to 'lyophilized cake' and the reconstitution of 'a lyophilized preparate' which occur in the passages extracted respectively in paragraphs 9 and 10 above describing the prior art, Dr Oppenheim agreed these reference were to material in a vial, that is, they were references to the drug as it was available in a hospital environment. Dr Brown also agreed that the reference to 'lyophilizate preparate' extracted in paragraph 10 above is a reference to the product available in the hospital environment.

45 I now turn to consider submissions in more detail. Mr Caine, of senior counsel, appearing for the applicants conceded that the term 'reconstituted' has a general meaning in the context of pharmaceutical sciences to describe the step of putting lyophilized material into solution. However, he submitted that 'reconstituted' was used also as a term of art in the context of cytotoxic drugs which meant the process of preparing a liquid dosage form of a cytotoxic drug before administration to a patient. He submitted that the essence of the invention is a reformulation of a known drug in a ready-to-use solution which was something that had never before been achieved. I agree with that description of the essence of the invention. He then submitted the context of the specification makes it clear that the phrase in contention in Claim 1 was a disclaimer in respect of the prior art. It was a reference to the lyophilised preparation, known at the priority date, which needed to be made up before administration.

46 It was further submitted that the process undertaken by the respondents is one in which a manufacturer produces a lyophilized material, in bulk, and supplies it to one of the Mayne entities, which then takes that freeze-dried, raw material and makes it into a ready-to-use solution. The applicants assert that the bulk lyophilization from the supplier entity is different from the prior art disclaimed and dealt with by the inventors in the Patent specification. Mr Caine's submissions are that the reconstitution referred to in the complete specification is reconstitution which involves a lyophilized cake in a vial; and that it is this specific reconstitution which is carved out from the definition of the monopoly of Claim 1.

47 The applicants submit that the complete specification refers to the dangers involved in the systems, as they were in 1985, being risks to the staff who had to reconstitute the lyophilized preparations shortly before administration because the preparations were unstable in solution over a longer period of time. This was the problem sought to be overcome through the invention of the ready-to-use solution. The invention did not involve the problematic process of reconstitution just prior to administration. Therefore, the applicants submit that the act of reconstitution just prior to administration is that which is sought to be disclaimed in Claim 1 through use of the phrase 'which has not been reconstituted from a lyophilizate.'

48 Mr Macaw, of senior counsel for the respondents, submitted that the words 'reconstituted from a lyophilizate' as occurring in Claim 1 bear an ordinary meaning and no special sense for them exists in the pharmaceutical industry, which would confine the meaning to a subset of their usual or ordinary meaning. It was contended that the meaning of the exclusionary integer of the claim including the word 'reconstituted' is plain and unambiguous, and in accordance with well-settled principle, the meaning of the exclusionary integer could not be qualified by resort to the body of the specification.

49 It was next submitted that even if resort were had to the body of the specification to clarify the expression in contention, such resort supports the ordinary meaning. Reliance was placed on the inventor's failure in the body of the specification to expressly state that 'lyophilized preparates' referred to in the body of the specification (about which Drs Brown and Oppenheim were cross-examined) were confined to what was known as at the priority date. Reliance was also placed on the fact that Claim 1 was not confined to a solution in a sealed container, as occurs in dependent Claim 2, and also placed on the fact that there was a

broad reference to containers in the body of the specification which was arguably not confined to vials or ampoules.

50 Further, the respondents relied on the consistory clause for the process in the body of the specification and the definition of the process in Claim 20 as it referred to 'anthracycline glycoside, which salt is not in the form of a lyophilizate' to support an argument that the dissolution of a salt was synonymous with 'reconstitution from a lyophilizate'.

THE SKILLED ADDRESSEE

51 As at the priority date the skilled addressee would have known that:

- anthracycline glycosides were well known compounds in the antineoplastic group of agents which were used widely as antitumour drugs;
- antineoplastic drugs, because of their toxicity, posed serious risks to persons handling them, whether manufacturing workers or pharmacists, medical personnel or nurses;
- the active ingredient in the solution was subject to stability problems with the attendant risk that the product deteriorated; and
- the lyophilized preparations, existing as at the priority date, for administration to cancer patients, came in the form of lyophilized cake in a vial, the lyophilized cake containing the active substance and an excipient.

52 The process of administration of the drug available at the relevant time was also known to the skilled addressee as follows:

- administration required reconstitution of the lyophilized cake and sometimes prolonged shaking was required to achieve complete dissolution; and
- commercially available anthracycline glycosides came in the abovementioned form.

53 It is necessary to apply well-settled principles concerning the proper construction of a patent specification and claims forming part of a complete specification. The court's task is

to make a 'commonsense assessment' of what the expression 'which has not been reconstituted from a lyophilizate', as used in Claim 1, conveys 'in the context of then-existing published knowledge': *Populin v H.B. Nominees Pty Ltd* (1982) 41 ALR 471 at 476.

54 Reference has already been made to the relevant observations in *Kimberly-Clark* at [24] that the court is *'to place itself in the position of some person acquainted with the surrounding circumstances as to the state of [the] art and manufacture at the time'*. As observed by Lockhart J in *Décor* at 391:

> *'The words used in a specification are to be given the meaning which the normal person skilled in the art would attach to those words, both in the light of his own general knowledge and in the light of what is disclosed in the body of the specification:* British Thomson-Houston Co Ltd v Corona Lamp Works Ltd *(1921) 39 RPC 49 per Viscount Haldane at 67, per Lord Shaw at 89;* Monsanto Co v Commissioner of Patents *(1974) 48 ALJR 59 per Stephen J at 60.'*

55 In *Décor*, at 400, Sheppard J distilled ten rules of construction from the authorities:

> *'(1) The claims define the invention which is the subject of the patent. These must be construed according to their terms upon ordinary principles. Any purely verbal or grammatical question that can be answered according to ordinary rules for the construction of written documents is to be resolved accordingly.*
>
> *(2) It is not legitimate to confine the scope of the claims by reference to limitations which may be found in the body of the specification but are not expressly or by proper inference reproduced in the claims themselves. To put it another way, it is not legitimate to narrow or expand the boundaries of monopoly as fixed by the words of a claim by adding to those words glosses drawn from other parts of the specification.*
>
> *(3) Nevertheless, in approaching the task of construction, one must read the specification as a whole.*
>
> *(4) In some cases the meaning of the words used in the claims may be qualified or defined by what is said in the body of the specification.*
>
> *(5) If a claim be clear, it is not to be made obscure because obscurities can be found in particular sentences in other parts of the document. But if an expression is not clear or is ambiguous, it is permissible to resort to the body of the specification to define or clarify the meaning of words used in the claim.*
>
> *(6) A patent specification should be given a purposive construction rather than a purely literal one.*
>
> *(7) In construing the specification, the court is not construing a written instrument operating inter partes, but a public instrument which must define a monopoly in such a way that it is not reasonably capable of being misunderstood.*
>
> *(8) The body, apart from the preamble, is there to instruct those skilled in*

> *the art concerned in the carrying out of the invention; provided it is comprehensive to, and does not mislead, a skilled reader, the language used is seldom of importance.*
>
> *(9) Nevertheless, the claims, since they define the monopoly, will be scrutinised with as much care as is used in construing other documents defining a legal right.*
>
> *(10) If it is impossible to ascertain what the invention is from a fair reading of the specification as a whole, it will be invalid. But the specification must be construed in the light of the common knowledge in the art before the priority date.'*

56 Particularly relevant are the principles that the specification as a whole must be read and the context of a specification may qualify the *prima facie* meaning of a word or expression in a claim. If a word used in a claim is not a term of art, by reference to the technical knowledge possessed by persons skilled in the art, and is used in a plain, clear and unambiguous way in a claim, there should be no resort to the body of the specification to aid in the construction of the claim: *Welch Perrin and Company Proprietary Limited v Worrel* (1960-1961) 106 CLR 588 at 610; *Electric & Musical Industries Ltd v Lissen Ltd* (1936) 54 RPC 23 at 41. That principle is subject to the proviso that any lack of clarity or ambiguity in a claim can be resolved by resort to the body of the specification: *Interlego AG v Toltoys Pty Ltd* (1973) 130 CLR 461 at 457/8 (per Barwick CJ and Mason J); *Décor* at 391; *Marconi v Mullard* (1923) 40 RPC 159 at 175.

57 There is no inconsistency in the principles governing construction of patent specifications as explained by Hely J in *Flexible Steel Lacing Co v Beltreco Ltd* (2000) 49 IPR 331 at [73] – [76] and especially [78]. It is as true of patent specifications, as of statutes (or any documents), as noted by Viscount Simonds in *Attorney-General v Prince Ernest Augustus of Hanover* [1957] AC 436:

> *'. . . words, and particularly general words, cannot be read in isolation: their colour and context are derived from context (at 461) . . . the elementary rule must be observed that no one should profess to understand any part of a statute or of any other document before he has read the whole of it. Until he has done so he is not entitled to say that it or any part of it is clear and unambiguous (at 463).'*

58 Similarly, the meaning of a word in a particular context may involve some limitation on its application in a patent claim, but such a meaning can only be derived from the context in which the word is used: see some examples, *Henriksen v Tallon* [1965] RPC 434 at 445 (per Reid LJ); *Minnesota Mining* at 261 ff, esp. 272 (per Aickin J) and *Décor* at 410-411

(per Sheppard J).

59 The word 'reconstituted' as it appears in the relevant expression in Claim 1 is not a term of art used to refer to the dissolution of a lyophilized product so as to produce a solution suitable for intravenous injection shortly thereafter. It is clear however that both the word 'reconstituted' and the expression of which it forms a part in Claim 1 are used in a special sense in the specification. Alternatively, because the word is capable of more than one meaning it lacks clarity. It is permissible to have resort to the body of the specification both to see whether a word or expression has a special meaning or whether it requires clarification because the ordinary, or usual, meaning is not sufficiently precise. To find a word or expression is used in a special sense it is only necessary that an intention to so use the word or expression is plainly indicated in the specification: *Minerals Separation North American Corp v Noranda Mines* (1952) 69 RPC 81 at 96.

60 The body of the specification shows the expression 'which has not been reconstituted from a lyophilizate' in Claim 1 disclaims preparations known in the prior art, the better to mark out the monopoly and to define the invention. References in the body of the specification to lyophilized preparations known as at the priority date were references to lyophilized preparations in a vial. Contextually, the exclusionary integer refers to a ready-to-use solution, produced from a lyophilizate in a vial which needed to be reconstituted before administration to a patient; that is what was known at the priority date and that is what is disclaimed by the exclusionary integer, so as to be excluded from the monopoly claimed for the invention. A reference in dependent Claim 20 to a process which is not confined expressly to such preparations does not detract from such a conclusion. Accordingly, the claim for infringement by reference to integer (5) of Claim 1 is made out.

61 It next becomes necessary to consider whether the respondents' product infringes by reference to integer (6)(ii) of Claim 1. In relation to a process used after August 2004, the respondents admit the pH has been adjusted to be within the stated range by use of a physiologically acceptable acid being hydrochloric acid. Accordingly, textual infringement has occurred in respect of product produced by that process.

62 An original process used before August 2004 involved production of certain product where the adjustment of the pH of the solution to within the range specified in Claim 1 was

achieved also by the use solely of hydrochloric acid. That product accordingly also constitutes a textual infringement. However, there was a third batch where after hydrochloric acid was used to adjust the pH of the solution to be within the claimed range of 2.5 – 5.0 (adjusted to 2.7 (or 2.8)) the respondents then added a minor amount of sodium hydroxide to further adjust the pH to 2.9. Thus there was no textual infringement with this product. However, the question in respect of an infringement of a combination patent is whether the essence or substance of an invention underlying its form has been taken, such that in substance and effect an infringement has occurred: *Clark v Adie* (1875) LR 10 Ch. App. 667 at 675 (per James LJ) referred to with approval by Dixon J in *Radiation Ltd v Galliers & Klaerr Pty Ltd* (1938) 60 CLR 36 at 51/52 (*'Radiation Ltd'*). There Dixon J eschewed literalism as an approach to assessing whether an alleged infringement fell within the language of the claim:

> *'But, on a question of infringement, the issue is not whether the words of the claim can be applied with verbal accuracy or felicity to the article or device alleged to infringed. It is whether the substantial idea disclosed by the specification and made the subject of a definite claim has been taken and embodied in the infringing thing.'*

That approach continues to apply unless the claims make it clear that the relevant area has been deliberately left out of the claim: *Olin Corporation v Super Cartridge Co Pty Ltd and Anor* (1977) 51 ALJR 525 at 530 (per Gibbs J); *Minnesota Mining* at 286 (per Aickin J). Immaterial variations will not escape infringement: *Populin* at 475.

63 In *Commonwealth Industrial Gases Ltd v MWA Holdings Pty Ltd* (1990) 180 CLR 160 (*'CIG'*) Menzies J dealt with a combination patent in respect of which a defendant consciously sought to avoid infringement by making a slight modification in manufacture to a particular part of a piece of equipment. He said at 167:

> *'Patent rights are not to be set at naught by such a subterfuge which . . . added nothing to the equipment and was made merely in an attempt to take full advantage of the invention while avoiding infringement of the plaintiff's letters patent by a modification so small as to be insignificant.'*

Menzies J went on to find the modification in manufacture did not avoid an essential feature because the defendant's product was so close as to still 'take the invention'.

64 The addition of a minor amount of sodium hydroxide, which avoids textual infringement in respect of integer 6(ii) is a modification so small as to be insignificant. The

consequence of adding a minor amount of sodium hydroxide was to produce water and sodium chloride both of which were already present in large quantities in the solution. The consequential variations in total water and sodium chloride present were within normal manufacturing tolerances. This is a modification which makes no material difference and in substance the invention is still taken. It cannot be said the modification was deliberately left outside the claim. Accordingly, the respondents' product for which the respondents use sodium hydroxide, in addition to hydrochloric acid, to adjust the pH is a product which is no different relevantly from the invention. Accordingly, the respondents do not thereby avoid infringement of Claim 1.

65 It needs to be mentioned that on this aspect of the dispute, the applicants relied on a principle of 'purposive' construction as advanced by Lord Diplock in *Catnic Components Ltd v Hill & Smith Ltd (No.1)* [1982] RPC 183 (*'Catnic Components'*), cited in numerous Australian cases. The respondents submitted there was no place for a purposive approach to construction on the facts of the case, because the word 'solely' in the relevant integer was a word of clear and ordinary meaning and because it is reasonable to infer the restriction was deliberate on the part of the patentee.

66 It has been recognised in numerous authorities that Lord Diplock was expounding the relevant common law rather than advancing any novel principle of infringement, as is made plain, in any event, in *Catnic Components* at 242/243: see *Kirin-Amgen Inc v Hoescht Marion Roussel Ltd* [2005] 1 All ER 667 at [33]-[35] and [42]-[43] (per Hoffman LJ); *Assidoman Multipack Limited (formerly Multipack Wraparound Systems) v Mead Corporation* [1995] RPC 321 at 330-333 (Aldous J); *PLG Research Ltd v Ardon International Ltd* [1995] RPC 287 at 309 (per Millett LJ). See also *Rhone-Poulenc Agrochinie SA v UIM* (1986) 12 FCR 477 at 498 (per Lockhart J); *Azuko Pty Ltd and Anor v Old Digger Pty Ltd (formerly SDS Digger Tools Pty Ltd)* (2001-2002) 52 IPR 75 at 99 (per Beaumont J); *Leonardis v Sartas No 1 Pty Ltd* (1996) 67 FCR 126 at 148 (per Burchett, Hill and Tamberlin JJ); *Nicaro Holdings Pty Ltd & Ors v Martin Engineering Co* (1989) 91 ALR 513 at 528/529 (per Gummow J); *Rehm Pty Ltd v Webster's Security Systems (International) Pty Ltd and Ors* (1988) 81 ALR 79 at 92 (Gummow J); *Martin Engineering Co v Trison Holdings Pty Ltd* (1989) 14 IPR 330 at 347/348 (Burchett J): *cf Root Quality Pty Ltd and Anor v Root Control Technologies Pty Ltd and Others* (2000) 177 ALR 231 at [39] and [44] (Finkelstein J) (*'Root Quality'*).

67 Lord Diplock suggests in *Catnic Components*, at 243:

> *'The question in each case is: whether persons with practical knowledge and experience of the kind of work in which the invention was intended to be used, would understand that strict compliance with a particular descriptive work or phrase appearing in the claim was intended by the patentee to be an essential requirement of the invention so that* any *variant would fall outside the monopoly claimed, even though it could have no material effect upon the way the invention worked.'*

68 Following that suggestion, Hoffman J in *Improver Corp v Remington Consumer Products Ltd* [1990] FSR 181 at 198 suggested that the court should ask itself, what have come to be known as the three *'Improver'* questions, as an aid to 'purposive' construction:

> *'(1) Does the variant have a material effect upon the way the invention works? If yes, the variant is outside the claim. If no –*
> *(2) Would this (i.e., that the variant had no material effect) have been obvious at the date of publication of the patent to a reader skilled in the art. If no, the variant is outside the claim. If yes -*
> *(3) Would the reader skilled in the art nevertheless have understood from the language of the claim that the patentee intended that strict compliance with the primary meaning was an essential requirement of the invention. If yes, the variant is outside the claim.'*

69 It is not necessary for the resolution of this case to do other than apply the Australian authorities referred to above. I note, however, that some Australian courts have derived assistance from the *Catnic Components* approach in deciding the ambit of the monopoly of a claim: see for example *Nesbit Evans Group Australia Pty Ltd v Impro Ltd and Anor* (1997) 39 IPR 56 and *Root Quality*. Had I regarded it as being of assistance to ask the *Improver* questions of the variant, the conclusion would have been that the variant is not outside the claim.

UK PATENT

70 A corresponding patent in the United Kingdom was the subject of a judgment of the English Court of Appeal dated 17 February 2005, reported as *Mayne Pharma Pty Ltd and Mayne Pharma plc v Pharmacia Italia SPA* [2005] EWCA Civ 137. The Mayne parties had sought a declaration of non-infringement in respect of Pharmacia's equivalent United Kingdom Patent 2,178,311 ('UK Patent'). A counterclaim for infringement followed and the issue, as here, was whether Mayne's product fell within Claim 1 (worded slightly differently). At first instance, a Deputy Judge found non-infringement. The Court of Appeal construed

Claim 1, as contended for by Pharmacia and upheld the appeal. On 10 March 2005 the Court of Appeal refused an application for leave to appeal to the House of Lords. A petition to the House of Lords directly for leave to appeal was then in prospect.

71 The applicants and respondents filed supplementary submissions dated, respectively, 24 and 11 March 2005. Essentially the applicants contended the principles of construction were consistent with those expressed in *Populin* and *Décor* and there was no basis upon which the position in Australia could be distinguished from that reached by the Court of Appeal.

72 The respondents drew attention to a distinction between Claim 1 in the Patent and Claim 1 in the UK Patent; the latter included the words 'injectable, ready-to-use' after the word 'An' at the beginning of Claim 1 and before the epithet 'sterile' in line 1.

73 The respondents noted in their submissions that in the United Kingdom the 'overarching principle of construction is contained in Article 69 of the European Patent Convention' and there is no equivalent to Article 69 in Australia. The compatibility between the principles of construction in Article 69 and the *Catnic Components* approach, (which stated the law applicable to the 1949 U.K. Act) is explained by Aldous J in *Assidoman* at 332-333, which explanation was approved in *Kirin-Amgen Inc* at [46] (per Hoffman LJ).

74 The respondents also relied on the fact that the process claims in the United Kingdom (claim 31) and Australia (claim 20) contained similar directions. The respondents urged again that the words in Claim 1 'which has not been reconstituted from a lyophilizate' refer to and include product which is reconstituted from a bulk lyophilizate at some point because the process claim is not limited to product which is reconstituted in a vial.

75 The decision of the English Court of Appeal is persuasive, to the extent that the complete specifications of the Patent and the UK Patent are very similar, although not identical, and there is a commonality of applicable principles.

76 It can be noted, however, that I have reached the conclusions set out above on the evidence before me and by applying principles as settled in the abovementioned Australian authorities. Orders will not be made today. The parties can prepare short minutes of final

orders on liability in accordance with these reasons and include any other orders or directions as appropriate for the further disposition of the matter.

I certify that the preceding seventy-six (76) numbered paragraphs are a true copy of the Reasons for Judgment herein of the Honourable Justice Crennan.

Associate: 

Dated: 5 August 2005

Counsel for the Applicant:	B Caine SC H Rofe
Solicitor for the Applicant:	Allens Arthur Robinson
Counsel for the Respondent:	R Macaw QC P Collinson
Solicitor for the Respondent:	Clayton Utz
Dates of Hearing:	27, 28, 29 & 30 September 2004 1 October 2004
Date of Judgment:	5 August 2005

EXHIBIT D

Federal Court of Canada | *Cour fédérale du Canada*

FACSIMILE TRANSMITTAL FORM | **FORMULAIRE D'ACHEMINEMENT PAR TÉLÉCOPIEUR**

TO

Name: Sheila Block

Title:

Organization: Torys

Location:

Facsimile No.: 416-865-7380

DESTINATAIRE

Nom: Susan Beaubien

Titre:

Organisme:

Endroit:

Télécopieur: 613-235-2508

FROM

Name: Steve Shepherd

Office: Federal Court

Telephone No.: 416 954-5052

Facsimile No.:

Date: December 20, 05

Time:

EXPÉDITEUR

Nom:

Bureau:

Téléphone:

Télécopieur:

Date:

Heure:

TOTAL NUMBER OF PAGES: (including this cover page)

NOMBRE DE PAGES: (incluant le présent formulaire)

COMMENTS

Please find attached the Order and Reasons for Order of the Court on file T-1142-04

REMARQUES

N.B.: If you do not receive all pages being transmitted, please call us at above number.

N.B.: S'il manque des pages, prière de communiquer avec l'expéditeur au numéro susmentionné.

Federal Court | Cour fédérale

CANADA

Date: 20051220

Docket: T-1142-04

Toronto, Ontario, December 20, 2005

PRESENT: THE HONOURABLE MR. JUSTICE ROGER T. HUGHES

BETWEEN:

PFIZER CANADA INC. and PHARMACIA ITALIA S.p.A.

Applicants

and

THE MINISTER OF HEALTH
and MAYNE PHARMA (CANADA) INC.

Respondents

ORDER

UPON APPLICATION made to this Court and heard on the 12th and 13th days of December, 2005, for an Order to prohibit the Minister of Health to issue a Notice of Compliance to the Respondent Mayne Pharma (Canada) Inc. in respect of an application therefore by said Respondent in respect of a certain drug containing epirubicin;

AND UPON reviewing the Record herein and hearing submissions of Counsel for the Applicant and the Respondent Mayne, The Minister taking no active part in these proceedings;

AND FOR the Reasons delivered herewith;

THIS COURT ORDERS that

1. The Minister of Health is prohibited from issuing a Notice of Compliance to Mayne Pharma (Canada) Inc. in respect of Epirubicin Hydrochloride Injection Ph. Eur. Having a strength per dosage unit of 2 mg/ml until the expiry of Canadian Letters Patent on October 22, 2008 or earlier if said patent is held to be invalid by an unappealable judgment of a competent Canadian Court; and

2. Counsel shall provide written submissions as to costs within ten (10) working days from the date hereof following which a further Order as to costs will be made.

"Roger T. Hughes"

JUDGE

Federal Court

CANADA

Cour fédérale

Date: 20051220

Docket: T-1142-04

Citation: 2005 FC 1725

BETWEEN:

PFIZER CANADA INC. and PHARMACIA ITALIA S.p.A.

Applicants

and

THE MINISTER OF HEALTH
and MAYNE PHARMA (CANADA) INC.

Respondents

REASONS FOR ORDER

HUGHES J.

[1] This is an application made under the provisions of the *Patented Medicines (Notice of Compliance) Regulations* SOR/93-133 as amended (the NOC Regulations). The Applicants Pfizer Canada Inc. and Pharmacia Italia S.p.A. (Pfizer) seek to the prohibit the Minister of Health (Minister) from issuing a Notice of Compliance under the Food and Drug Regulations to Mayne Pharma (Canada) Inc. (Mayne) in respect of its proposed injectable ready-to-use Epirubicin Hydrochloride solution in a strength of 2mg/ml (Mayne Product) until the expiry of Canadian Patent 1,291,037 ('037 Patent). Pfizer also seeks a declaration that Mayne did not serve a proper notice of allegation as required by the NOC Regulations, costs and other relief.

[2] The '037 patent was issued and granted by the Canadian Patent Office on October 22, 1991 from an application filed in Canada on June 27, 1986. As such the '037 Patent falls to be considered under the "*old*" provisions of the *Patent Act*, R.C.S. 1989, c.P.4 as they pertain to patents granted in respect of applications filed in Canada before October 1, 1989. This patent is concerned with injectable solutions used to treat tumours. It contains 116 claims which can be divided into three categories 1) product claims directed to ready-to-use solutions; 2) process claims directed to the making of such solutions; and 3) use claims directed to the use of such solutions. Of the product claims, claims 1 (and dependent claims 2-11), 12 (and dependent claims 13-22), 60 (and dependent claims 61-68), 69 (and dependent claims 70-88) and 98 (and dependent claims 99-105 and 115) are at issue. Of the use claims, claims 47 and 59 are at issue. By reason of the nature of the NOC Regulations, no process claims are at issue.

[3] The Applicants Pfizer are "*first parties*" as defined by the NOC Regulations. There is no dispute that the '037 patent has been properly listed in accordance with those Regulations.

[4] The Respondent Mayne is a "*second party*" as defined in the NOC Regulations. Mayne has, in its letter of allegation, stated that it is seeking a Notice of Compliance under the Food and Drug Regulations from the Minister for Epirubicin Hydrochloride Injection Ph. Eur. having a strength per dosage unit of 2 mg/ml (Mayne Product). Mayne alleges that no claim of the '037 patent will be infringed by the Mayne Product, the process for its manufacture and its route of administration for use. The letter of allegation states as follows:

3. *The Mayne Product that is subject of the abbreviated new drug submission which has been filed and is pending with the Minister of Health, is formulated as a ready to use injectable solution in a single dose, sealed vial (10 mg/5ml, 50 mg/ml, 200 mg/ml). The Mayne Product comprises the following ingredients: the active pharmaceutical ingredient (API) Epirubicin Hydrochloride [which has been reconstituted from lyophilized Epirubicin Hydrochloride (Ph. Eur.) manufactured and supplied to Mayne by a third party]; Water for Injection (Ph. Eur.); Sodium Chloride (Ph. Eur.); and Hydrochloric Acid (Ph. Eur.) [for pH adjustment within the range 2.5 to 4.0, if necessary]. Nitrogen (Ph. Eur) is present to deoxygenate the Water for Injection and to provide an inert headspace within the vial.*

4. *The Mayne Product will be manufactured by Mayne's Australian parent (Mayne Pharma Pry.) using the following process:*

   (a) *65% of the required volume of Water for Injection (Ph. Eur) is added to a mixing vessel and purged with Nitrogen (Ph. Eur) fro 15 minutes. [Solution A]*

   (b) *A slurry of Epirubicin Hydrochloride is prepared by reconstituting lyophilized Epirubicin Hydrochloride (Ph. Eur) with Water for Injection (Ph. Eur) to form a slurry. The slurry is added to the Solution A described above while stirring. The solution is mixed for 30 minutes.*

   (c) *10% of the required volume of Water for Injection (Ph. Eur) is added to a second mixing vessel and purged with Nitrogen (Ph. Eur) for 15 minutes. Sodium chloride (Ph. Eur) is added to the Water for Injection (Ph. Eur) while stirring. The solution is mixed for 10 minutes [Solution B] Potency of the solution may be checked and the addition of Water forInjection may be adjusted, as necessary.*

   (d) *Solution B is added to Solution A and stirred for 10 minutes. The pH of the resultant bulk solution is checked and adjusted, if necessary, to a target range of 2.8 to 3.0 with Hydrochloric Acid, (Ph. Eur).*

   (e) *Thereafter, the volume of the bulk solution is progressively adjusted to 100% of the volume necessary for an epirubicin hydrochloride drug concentration of 2 mg/ml with addition of Water for Injection (Ph. Eur). The pH of the solution is checked and, if necessary, the pH of the solution is adjusted to the target range of 2.8 to 3.0 with Hydrochloric Acid (Ph. Eur).*

   (f) *The solution is then passed through a sterilizing filter, and aseptically dispensed into sterile, glass vials under a nitrogen atmosphere. The vials are then stoppered and sealed.*

5. *The route of administration for the Mayne Product is intravenous.*

[5] Pfizer does not dispute the accuracy of these representations.

[6] The only issue in these proceedings is that of infringement, validity of the '037 patent is not challenged. The issue of infringement turns on a question of construction of the claims and in particular, to what does the phrase "*not reconstituted from a lyophilizate*" refer in construing the claims. In this regard it is sufficient, for illustration, to refer to claim 1, a broad product claim, and claim 47 a broad use claim.

> *1. An injectable, ready-to-use, sterile, pyrogen-free, anthracycline glycoside solution which consists essentially of a physiologically acceptable salt of an anthracycline glycoside dissolved in a physiologically acceptable aqueous solvent therefore at an anthracycline glycoside concentration of from 0.1 to 50 mg/ml, which has not been reconstituted from a lyophilizate and the pH of which has been adjusted to from 2.5 to 5.0 solely with a physiologically acceptable acid.*
>
> ***
>
> *47. Use of an injectable, ready-to-use, sterile pyrogen-free solution as defined in claim 1 to inhibit the growth of a tumour selected from sarcomas, carcinomas, lymphomas, neuroblastoms, melanoma, mycloma, leukemias and wilms tumour.*

[7] The other claims at issue differ in detail, which detail is not material to the issue before this Court. I accept those differences as enumerated in the Beijnen affidavit filed herein at paragraphs 29 to 33 and 35.

> *29. Claim 12 claims the same solution as in claim 1, except that the pH of the solution is adjusted with a physiologically acceptable acid selected from a group that includes hydrochloric acid.*
>
> ***
>
> *30. Claim 60 claims a solution which is the same as the solution in claim 1, except that it is storage stable and has a narrower pH range.*
>
> ***

31. *Claim 69 claims a solution which is the same as the solution in claim 12, except that it is storage stable and has a narrower pH range.*

***

32. *Claim 98 claims a solution which is the same as the solution in claim 69, except that the pH of the solution has been adjusted from 2.5 to 3.5 solely with a glycine buffer.*

33. *There are also various dependent solution claims, which include the following:*

(a) *an anthracycline glycoside salt solution in a sealed container (claims 2, 13, 61, 70 and 99);*

(b) *a solution of an epirubicin salt (claims 3, 14, 62, 71 and 100);*

(c) *a solution of an epirubicin salt in a sealed container (claims 63, 72 and 101);*

(d) *a solution of epirubicin hydrochloride (claims 4, 15, 64 and 73);*

(e) *an anthracycline glycoside salt solution having a pH of from 2.62 to 3.14 (claims 5 and 16), or from 2.6 to 3.5 (claims 65 and 74) or of about 3 (claims 6, 17 and 102); and*

(f) *a solution in which the concentrations of the anthracycline glycoside is from 1 mg/ml to 20 mg/ml (claims 9, 20, 68, 77 and 105).*

***

35. *Claims 47 and 59 of the '037 Patent are the use claims. They cover the use of the solutions described in solution claims 1 and 12. The use claims read as follows:*

> *Use of an injectable, ready-to-use, sterile, pyrogen-free solution as defined in claim (1 or 12, in claims 47 and 59*

respectively) to inhibit the growth of a tumour selected from sarcomas, carcinomas, lymphomas, neuroblastoma, melanoma, myeloma, leukaemias and Wilms tumour.

[8] The process claims are not at issue in these proceedings. The NOC Regulations do not extend to processes. However claim 36, the broadest of the process claims, should be noted. It reads:

> *36. A process for producing an injectable, ready-to-use, sterile, pyrogen-free, anthracycline glycoside solution which consists essentially of a physiologically acceptable salt of an anthracycline glycoside dissolved in a physiologically acceptable aqueous solvent therefore, which has not been reconstituted from a lyophilizate and which has a pH of from 2.5 to 5.0, which process comprises dissolving the said physiologically acceptable salt, which salt is not in the form of a lyophilizate, in the said solvent at an anthracycline glycoside concentration of from 0.1 to 50 mg/ml; adding solely a physiologically acceptable acid to adjust the pH to from 2.5 to 5.0 as desired and passing the resulting solution through a sterilising filter.*

[9] The other process claims are directed to narrowing parameters similar to the solution claims.

[10] The issue in this proceeding is one of construction of the claims. The answer as to infringement will be apparent once the claims are construed. Construction is a matter for the Court alone, to be done before consideration is given to issues of infringement or validity, it is not to be "*results oriented*", one and the same interpretation applies to validity and infringement issues (*Whirlpool Corp.* v. *Camco Inc*, [2000] 2 S.C.R. 1067 at paras. 43 and 49(a) and (b)). Onus does not come into play at the construction stage of a patent proceeding.

[11] For the purposes of the construction issue in this proceeding the claims can be divested of their more technical terms and presented more simply. One of the more technical terms is that of lyophilization which, in everyday terms can be expressed as freeze drying. A benefit of such freeze drying is that it enhances the shelf life of the product. A detriment is that it must be reconstituted, by mixing with a suitable solvent, before use.

Solution Claims:

An injectable, ready-to-use solution which consists essentially of a salt of the active ingredient dissolved in an acceptable solvent at a given range of concentration, which has not been reconstituted from a lyophilizate and the pH of which has been adjusted to a certain range solely with an acceptable acid

Use claims:

Use of an injectable, ready-to-use solution to inhibit the growth of certain tumours.

Process Claims (not at issue in this NOC proceeding):

A process for producing an injectable, ready-to-use solution as described in the solution claims, comprising dissolving the salt, which salt is not in the form of a lyophilizate in the solvent to a certain concentration; adding solely an acceptable acid to adjust the pH to a certain range and filtering.

[12] Pfizer argues that the words "*not reconstituted from a lyophilizate*" in the solution claims and, by implication in the use claims, refer to the final product as it is presented to the medical professional for administration to a patent. Mayne on the other hand argues that those words refer to the salt of the active ingredient anthracycline glycoside. Given Pfizer's construction the Mayne Product and its use, would infringe the claim at issue; given Mayne's construction, they would not.

[13] The Court is aware that these issues have already been litigated by the parties or entities related to them, in the United Kingdom and Australia. Those decisions can be located at:

> **UK** – *Mayne Pharma Pty Ltd.* v. *Pharma Italia SpA*, [2004] EWHC 2458 (Ch.) a decision dated 1 November 2004, by Wyand Q.C. a Deputy Judge which was reversed by the Court of Appeal in [2005] EWCA Civ 317, on February 1, 2005, judgment for that Court given by Jacob L.J. Leave to appeal in the House of Lords was refused.
>
> **Australia** – *Pharmacia Italia SpA* v. *Mayne Pharma Pty Ltd*, [2005] F.C.A. 1078 and [2005] F.C.A. 1675. Decisions of the Federal Court of Australia. No appeal has been taken from these decisions, and, I am informed, none is now possible.

[14] These decisions are not binding upon this Court.

[15] This case rests simply on the question of claim construction. For that purpose I propose to examine, briefly, the history of claim construction in Canada and the United Kingdom. Then I will address the principals to be applied in construing a claim as instructed by the Supreme Court of Canada in *Whirlpool* (*Whirlpool Corp.* v. *Camco Inc.* [2000] 2 S.C.R. 1067) and *Free World* (*Free World Trust* v. *Electro Santé Inc.* [2000] 2 S.C.R. 1024). Then I propose to construe the claims at issue.

The History of Claim Construction

[16] In the earliest of days in patent history, a patent did not contain claims as we know them. A patent may have ended with a phrase such as "*A device substantially as described herein*". A good summary was given by Blanco White in "*Patents for Inventions*", 4th ed, London, Stevens & Sons 1979 at paragraph 1-305:

> ***Origin and growth of claims***
>
> *In such circumstances there was not room for the modern system of patent claims. The patentee quite often did, during the nineteenth century, end his specification with an indication of the features of his invention he considered new and important ("and what I claim is the levers x and y, co-operating with the wheel b and rod c," or something like that)-much as the proprietor of a design today makes a statement of the features of novelty claimed for his design. It was not until the 1883 Act that the inclusion of claims was compulsory, and it was not until the transfer of the key jurisdiction in patent actions from the jury of a court of common law to the Court of Chancery and the Chancery Division had resulted in the growth of rules for determining how to construe a principle of operation out of the description of a machine that we find claims in the modern sense growing up. For the essence of modern claim is that the patentee no longer leaves it to the jury to determine the scope of his invention, but tries to set this out for himself in his claims. By now it is a commonplace that this is precisely what claims are for, but it was not a commonplace seventy years ago; it was not even clear law that claims had that effect, until the famous decisions in Nobel v. Anderson in 1894 made it so. Nor until the second decade of the present century was it clear that a patentee who wished to cover the principle of operation of his machine, and not only the details of its construction, must say so in his claims and not just leave it to the jury. Thus it is hardly necessary to go back more than fifty years in the Reports of Patent Cases to find the distinction between the invention claimed and the preferred embodiment of it described in detail in the specification, which is so fundamental to present-day ideas, either not drawn at all or drawn only in vague and ambiguous terms. Since a judicial decision does not lose its authority by becoming obsolete-rather it gains in sanctity-the law is still bedevilled by authoritative judgments delivered before the days of claims.*

[17] The bedevilling of the law by the ghosts of these earlier, pre-claim, cases is evident in the cri de coeur of Lord Loreburn in *Natural Colour Kinematograph Co. Ltd.* v. *Bioschemes Ltd*, (1915) 32 R.P.C. 256 (H.L.) at page 266 where he speaks of counsel shaping and re-shaping a claim with references to the specification and other evidence:

> *I wish to add that, quite apart from these grounds, I think this Patent is bad from ambiguity in the Specification. There seems to be some danger of the well known rule of law against ambiguity being in practice invaded. Some of those who draft Specifications and Claims are apt to treat this industry as a trial of skill, in which the object is to make the Claim very wide upon one interpretation of it, in order to prevent as many people as possible from competing with the patentee's business and then to rely upon carefully prepared sentences in the Specification which, it is hoped, will be just enough to limit the Claim within safe dimensions if it is attacked in Court. This leads to litigation as to the construction of Specifications, which could generally be avoided if at the outset a sincere attempt were made to state exactly what was meant in plain language. The fear of a costly law suit is apt to deter any but wealthy competitors from contesting a Patent. This is all wrong. It is an abuse which a Court can prevent, whether a charge of ambiguity is or is not raised on the Pleadings, because it affects the public by practically enlarging the monopoly, and does so by a kind of pressure which is very objectionable. It is the duty of patentee to state clearly and distinctly, either in direct words or by clear and distinct reference, the nature and limits of what he claims. If he uses language which, when fairly read, is avoidably obscure or ambiguous, the Patent is invalid, whether the defect be due to design, or to carelessness or to want of skill. Where the invention is difficult to explain, due allowance will, of course, be made for any resulting difficulty in the language. But nothing can excuse the use of ambiguous language when simple language can easily be employed, and the only safe way is for the patentee to do his best to be clear and intelligible. It is necessary to emphasize this warning. To my mind, this is a very plain case of offence against the rule to which I have referred. I cannot see what purpose there could have been using the roundabout language here employed, which has provoked so much argumentative subtlety and taken up so much time, unless the object was to hold in reserve a variety of constructions for use if the Patent should be called in question, and in the meantime to frighten off those who might be disposed to challenge the Patent.*

[18] The same sentiment was expressed by the United States Supreme Court in the '*nose of wax*" case, *White* v. *Dunbar*, 119 US 47 (1886) per Bradley J. at pp 51-52 as cited by the Supreme Court of Canada in the *Whirlpool* case, supra, at paragraph 51:

> *Some persons seem to suppose that a claim in a patent is like a nose of wax which may be turned and twisted in any direction, by merely referring to the specification, so as to make it include something more than, or something different from, what its words express... . The claim is a statutory requirement, prescribed for the very purpose of making the patentee define precisely what his invention is; and it is unjust to the public, as well as an evasion of the law, to construe it in a manner different from the plain import of its terms.*

a) In Canada

[19] As matters developed in Canada, the Court would not, typically, first attempt to construe a claim, rather, it would go first to either validity or infringement and apply what was described as a "*literal*" reading of the claim. If the claim survived validity on a "*literal*" reading, then infringement would be considered "*literally*" and if there was no such infringement, then a second look at the claims on the basis of the "*substance*" was taken, as infringement was considered either literally or in substance. A good example of this practice in *Kramer* v. *Lawn Furniture Inc.* (1974), 13 C.P.R. (2nd) 231 a decision of Addy J. of the Federal Court. At pages 235 and 236 he found the patent to be valid without any discussion as to how the claim was to be construed. He then turned to infringement at page 237 and gave a classic statement as to claim interpretation:

> *The claims should be interpreted by reading them and applying common vocabulary of the art to the wording of the claim. They should be interpreted as if read by a person who is possessed of all the technical knowledge required to fully understand the terms used and the principles involved. The specifications and drawings should be read as a whole to provide background to assist in the interpretation of the claim or to supply the vocabulary necessary for the interpretation of the claim but should not be used to vary or enlarge the claims, except in so far as the vocabulary, as supplied by the specifications, reasonably and fairly provides for such a variation or enlargement. As has been often stated, the patentee may act as his own lexicographer.*

[20] Having given that statement, he said at page 238:

> *In the light of these general principles, the text of the claims of the plaintiffs' two patents must be examined to see, first, if there has been a literal infringement of the patents as expressed in the claims and, if not, then whether there has nevertheless been a true infringement of the substance of the inventions.*

[21] He then examined infringement on a "*literal*" interpretation of the claims and, finding none, embarked on a consideration of the "*substance*" of the claim. At page 239 he said:

> *Although there is no literal infringement, the Court must also determine whether the variations are minor ones and whether the alleged infringer has in fact taken the substance of the invention, refer Omark Industries (1960) Ltd. v. Gouger Saw Chain Co. et al., supra; whether the object under attack is but a colourable imitation of the invention, refer Fox's Canadian Law and Practice Relating to Letters Patent for Inventions, 4th ed. (1972), at pp. 364-9 and whether the defendant has in effect taken what has been described in the cases as the pith and marrow of the patent or invention.,*

[22] The "*two step*" approach respecting infringement was conflated to one by the Federal Court of Appeal in the *Mobil Oil* case (*Mobil Oil Corp.* v. *Hercules Canada Inc* (1995), 63 C.P.R. (3rd) 473) where Marceau J. for the Court said at page 488:

> *The established law in Canada, as stated long ago by Thorson P. in McPhar Engineering Co. v. Sharpe Instruments Ltd. (1960), 35 C.P.R. 105, [1956-60] Ex. C.R. 447, 21 Fox Pat. C. 1 (Ex. Ct.), is "that if a person takes the substance of an invention he is guilty of infringement and it does not matter whether be omits a feature that is not essential to it or substitutes an equivalent for it". That being the case, I do not appreciate the utility of the traditional twofold test and even its relevance. No doubt a textual infringement will simplify the problem as it will put an immediate end to the inquiry. But it seems to me that the exercise may be useless in cases like this one where the distinction between textual and substantial infringement may be difficult to draw.*

[23] As an "*outlier*" to the main stream of thought, there are a few cases, notable of which is *Schweyer Electric and Mfg Co.* v. *New York Central Railroad Co.* [1935] S.C.R. 665 where the Supreme Court took claims directed to electrically operated railroad signal devices without reference to whether or not alternating current was to be used and, by reading the specification found that the claims "*inevitably*" meant alternating current. Per Duff C.J. for the Court at 669:

> *In construing these claims they must be read with reference to the earlier part of the specification and, so reading them, it seems to me the conclusion is inevitable -- I am convinced this is not putting it too strongly -- that, as regards the devices in the apparatus on the vehicle which respond to the "caution" and "danger" signals, these claims do not contemplate a system which could be effectively worked without the use of alternating current circuits. In that view, since the respondents employ direct current circuits alone, no infringement is established.*

b) In the United Kingdom

[24] Claim construction has come to its current state in the United Kingdom in two cases. The first, *Catnic* (*Catnic Components Limited* v. *Hill and South Limited* [1982] R.P.C. 183 with the House of Lords decision starting at 239) was reviewed by the Supreme Court of Canada in *Whirlpool* supra. The second is more recent and after *Whirlpool*. It is *Kirin-Amgen Inc.* v. *Hoechst Marion Roussel Ltd.* a 2004 decision of the House of Lords reported, in Canada, at 331 N.R.1.

[25] *Catnic* was a breakthrough in that it did away with the two part approach – textual then pith and marrow – and replaced it with one criteria "*purposive construction*." It should be noted, however, that this was done in the context of an infringement analysis only and, rather than being directed to the claim alone, the House of Lords speaks of an "*invention*" and a "*patent specification*". Lord Diplock at pages 242 and 243 says:

> *My Lords, in their closely reasoned written cases in this House and in the oral argument, both parties to this appeal have tended to treat "textual infringement" and infringement of the "pith and marrow" of an invention as if they were separate causes of action, the existence of the former to be determined as a matter of construction only and of the latter upon some broader principle of colourable evasion. There is, in my view, no such dichotomy; there is but a single cause of action and to treat it otherwise, particularly in cases like that which is the subject of the instant appeal, is liable to lead to confusion.*
>
> ***
>
> *My Lords, a patent specification is a unilateral statement by the patentee, in words of his own choosing, addressed to those likely to have a practical interest in the subject matter of his invention (i.e. "skilled in the art"), by which he informs them what he claims to be the essential features of the new product or process for which the letters patent grant him a monopoly. It is those novel features only that he claims to be essential that constitute the so-called "pith and marrow" of the claim. A patent specification should be given a purposive construction rather than a purely literal one derived from applying to it the kind of meticulous, verbal analysis in which lawyers are too often tempted by their training to indulge. The question in each case is: whether persons with practical knowledge and experience of the kind of work in which the invention was intended to be used, would understand that strict compliance with a particular descriptive word or phrase appearing in a claim was intended by the patentee to be an essential requirement of the invention so that any variant would fall outside the monopoly claimed, even though it could have no material effect upon the way the invention worked.*

[26] By the time the *Kirin- Amgen* decision was made by the House of Lords, the United Kingdom had adhered to the European protocol respecting patents and article 69 of the protocol became important. It reads:

> *Article 69*
>
> *Extent of protection*
>
> *(1) The extent of the protection conferred by a European patent to a European patent application shall be determined by the terms of the claims. Nevertheless, the description and drawings shall be used to interpret the claims.*

> *(2) For the period up to grant of the European patent, the extent of the protection conferred by the European patent application shall be determined by the latest filed claims contained in the publication under Article 93. However, the European patent as granted or as amended in opposition proceedings shall determine retroactively the protection conferred by the European patent application, insofar as such protection is not thereby extended.*

[27] This article, it should be noted, does not differ materially from what has become standard Canadian practice namely, reading the claims in the context of the whole of the specification, a point which the Supreme Court of Canada makes at paragraph 50 of the *Whirlpool* decision.

[28] In *Kirin- Amgen*, Lord Hoffman, with whom the other Lords agreed, gave a *tour de force* as to patent construction which bears repeating here. In brief, he said as to construction that is *objective*, it is concerned with what a reasonable person, here the reasonable person skilled in the art to which the patent pertains, would have understood the author (inventor) to mean. The question is not what the inventor might have intended but rather what the addressee understands. Lord Hoffman said at paragraphs 32 to 35:

> *32. Construction, whether of a patent or any other document, is of course not directly concerned with what the author meant to say. There is no window into the mind of the patentee or the author of any other document. Construction is objective in the sense that it is concerned with what a reasonable person to whom the utterance was addressed would have understood the author to be using the words to mean. Notice, however, that it is not, as is sometimes said, "the meaning of the words the author used", but rather what the notional addressee would have understood the author to mean by using those words. The meaning of words is a matter of convention, governed by rules, which can be found in dictionaries and grammars. What the author would have been understood to mean by using those words is not simply a matter of rules. It is highly sensitive to the context of and background to the particular utterance. It depends not only upon the words the author has chosen but also upon the identity of the audience he is taken to have been addressing and the knowledge and assumptions which one attributes to that audience.*
>
> ***
>
> *33. In the case of a patent specification, the notional addressee is the person skilled in the art. He (or, I say once and for all, she) comes to a reading of the specification with common general knowledge of the art. And he reads the specification on the assumption that its purpose is to both to describe and to demarcate an invention - a practical idea which the patentee has had for a new product or process - and not to be a textbook in mathematics or chemistry or a shopping list of chemicals or hardware. It is this insight which lies at the heart of "purposive construction". If Lord Diplock did not invent the expression, he certainly gave it wide currency in the law. But there is, I think, a tendency to regard it as a vague description of some kind of divination which mysteriously penetrates beneath the language of the*

specification. Lord Diplock was in my opinion being much more specific and his intention was to point out that a person may be taken to mean something different when he uses words for one purpose from what he would be taken to mean if he was using them for another. The example in the Catnic case was the difference between what a person would reasonably be taken to mean by using the word "vertical" in a mathematical theorem and by using it in a claimed definition of a lintel for use in the building trade. The only point on which I would question the otherwise admirable summary of the law on infringement in the judgment of Jacob LJ in Rockwater Ltd v Technip France SA (unreported) [2004] EWCA Civ 381, at paragraph 41, is when he says in sub-paragraph (e) that to be "fair to the patentee" one must use "the widest purpose consistent with his teaching". This, as it seems to me, is to confuse the purpose of the utterance with what it would be understood to mean. The purpose of a patent specification, as I have said, is no more nor less than to communicate the idea of an invention. An appreciation of that purpose is part of the material which one uses to ascertain the meaning. But purpose and meaning are different. If, when speaking of the widest purpose, Jacob LJ meant the widest meaning, I would respectfully disagree. There is no presumption about the width of the claims. A patent may, for one reason or another, claim less than it teaches or enables.

34. "Purposive construction" does not mean that one is extending or going beyond the definition of the technical matter for which the patentee seeks protection in the claims. The question is always what the person skilled in the art would have understood the patentee to be using the language of the claim to mean. And for this purpose, the language he has chosen is usually of critical importance. The conventions of word meaning and syntax enable us to express our meanings with great accuracy and subtlety and the skilled man will ordinarily assume that the patentee has chosen his language accordingly. As a number of judges have pointed out, the specification is a unilateral document in words of the patentee's own choosing. Furthermore, the words will usually have been chosen upon skilled advice. The specification is not a document inter rusticos for which broad allowances must be made. On the other hand, it must be recognised that the patentee is trying to describe something which, at any rate in his opinion, is new; which has not existed before and of which there may be no generally accepted definition. There will be occasions upon which it will be obvious to the skilled man that the patentee must in some respect have departed from conventional use of language or included in his description of the invention some element which he did not mean to be essential. But one would not expect that to happen very often.

35. One of the reasons why it will be unusual for the notional skilled man to conclude, after construing the claim purposively in the context of the specification and drawings, that the patentee must nevertheless have meant something different from what he appears to have meant, is that there are necessarily gaps in our knowledge of the background which led him to express himself in that particular way. The courts of the United Kingdom, the Netherlands and Germany certainly discourage, if they do not actually prohibit, use of the patent office file in aid of construction. There are good reasons: the meaning of the patent should not change according to whether or not the person skilled in the art has access to the file and in any case life is too short for the limited assistance which it can provide. It is however frequently impossible to know without access, not merely to the file but to the private thoughts of the patentee and his advisors as well, what the reason was for some apparently inexplicable limitation in the extent of the monopoly claimed. One possible explanation is that it does not represent what the patentee really meant to say. But another is that he did mean it, for reasons of his own; such as wanting to avoid arguments with the examiners over enablement or prior art and have his patent granted as soon as possible. This feature of the practical life of a patent agent reduces the scope for a conclusion that the patentee could not have meant what the words appear to be saying. It has been suggested that in the absence of any explanation for a restriction in the extent of protection claimed, it should be presumed that there was some good reason between the patentee and the patent office. I do not think that it is sensible to have presumptions about what people must be taken to have meant but a

> *conclusion that they have departed from conventional usage obviously needs some rational basis.*

The Principles of Whirlpool and Free World

[29] The Supreme Court of Canada in *Whirlpool* and *Free World* supra, gave landmark decisions respecting Canadian patent law. While preceding *Kirin- Amgen* by almost four years, these decisions are remarkably in agreement. In its decisions the Supreme Court endorsed the "*purposive construction*" approach and did away with the "*two tiered*" approach (*Free World* paras 45-50, *Whirlpool* paras 42-50). The Court expressly rejected a "*grammatical*" or "*meticulous verbal analysis*" approach (*Whirlpool* paragraphs 48 and 53).

[30] These two cases, together with *Kirin-Amgen* provide instruction as to the construction of a claim in a "*purposive*" manner.

Statutory Basis in Canada

[31] Section 34(2) of the *Patent Act* R.S.C. 1985, c.P.4 requires that a patent specification and with a claim or claims which "*distinctly and in explicit terms*" set out the scope of the monopoly claimed. As the Supreme Court in *Whirlpool* said at paragraph 42:

> *42 The content of a patent specification is regulated by s. 34 of the Patent Act. The first part is a "disclosure" in which the patentee must describe the [page1089] invention "with sufficiently complete and accurate details as will enable a workman, skilled in the art to which the invention relates, to construct or use that invention when the period of the monopoly has expired": Consolboard Inc. v. MacMillan Bloedel (Sask.) Ltd., [1981] 1 S.C.R. 504, at p. 517. The disclosure is the quid provided by the inventor in exchange for the quo of a 17-year (now 20-year) monopoly on the exploitation of the invention. The monopoly is enforceable by an array of statutory and equitable remedies and it is therefore important for the public to know what is prohibited and where they may safely go while the patent is still in existence. The public notice function is performed by the claims that conclude the specification and must state "distinctly and in explicit terms the things or combinations that the applicant regards as new and in which he claims an exclusive property or privilege" (s. 34(2))". An inventor is not obliged to claim a monopoly on everything new, ingenious and useful disclosed in the specification. The usual rule is that what is not claimed is considered disclaimed.*

The Questions to be Addressed in Construing a Claim

[32] When construing the claims, therefore, the following questions may be addressed:

1. Who construes the claims?
2. When are the claims construed?
3. As of what date is the claim to be construed?
4. What are the criteria for construction?
5. What resources may be used for purposes of construction?
6. Through whose eyes is construction to be made?
7. What is to be made of the resulting construction?

1) Who Construes the Claim

[33] The Court construes the claim (*Whirlpool* at paragraphs 43 and 45).

[34] It is not the function of an expert witness to construe the claim. As the Supreme Court said at paragraph 57 of *Whirlpool*:

> *"The role of the expert was not to interpret the patent claims but to put the trial judge in the position of being able to do so in a knowledgeable way."*

2) When are the Claims Construed

[35] The claims are construed by the Court at the outset of its decision before considering issues of validity or infringement. It is not to be a "*results oriented*" exercise, rather, it is to be carried out without an eye either to the alleged infringement or the prior art. (*Whirlpool* paragraphs 43 and 49(a)).

3) As of What Date are the Claims to be Construed

[36] The claims are to be construed as of the date of the patent was issued and granted in the case of an "*old*" *Act* patent, that is, one that was applied for in Canada before October 1, 1989. In respect of a "*new*" *Act* patent, that is, one for which an application was filed in Canada after October 1, 1989, the date upon which the claim is to be construed is the publication date. (*Whirlpool* paragraph 42, *Free World* paragraph 44).

4) What are the Criteria for Construction

[37] In this regard consideration must be given to the words of the Supreme Court in *Whirlpool* at paragraph 45:

> *"The key to purposive construction is therefore the identification by the court, with the assistance of the skilled reader, of the particular words or phrases in the claims that describe what the inventor considered to be the "essential" elements of his invention."*

[38] In Free World in paragraph 51 the Supreme Court says:

> *"The words chosen by the inventor will be read in the sense the inventor is presumed to have intended."*

[39] These words do not mean that the Court is to embark upon a *subjective* examination of what was in the mind of the inventor, rather, the Court is to embark upon an *objective* exercise as to what a skilled reader would have understood the inventor to mean. As Lord Hoffman said at paragraph 32 of *Kirin- Amgen*:

> *"Construction is objective in the sense that it is concerned with what a reasonable person to whom the utterance was addressed would have understood the author to be using the words to mean (emphasis added)."*

5) What Resources May be Used for Construction

[40] A claim is to be read in the context of the rest of the specification. As the Supreme Court said in *Whirlpool* at paragraph 48:

> *48 ... In Catnic, as in the earlier case law, the scope of the monopoly remains a function of the written claims but, as before, flexibility and fairness is achieved by differentiating the essential features ("the pith and marrow") from the unessential, based on a knowledgeable reading of the whole specification through the eyes of the skilled addressee rather than on the basis of "the kind of meticulous verbal analysis in which lawyers are too often tempted by their training to indulge" (Catnic, supra, p. 243).*

at paragraph 49(f):

> *49(f) While the appellants express concern that "purposive construction" may open the door to extrinsic evidence of intent, as is the case with certain types of extrinsic evidence in the United States, neither Catnic, supra, nor O'Hara, supra, goes outside the four corners of the specification, and both properly limit themselves to the words of the claims interpreted in the context of the specification as a whole.*

and at paragraph 52:

> *52 I have already given my reasons for concluding that to the extent the appellants are arguing for a simple "dictionary" approach to construction of the '803 claims, it must be rejected. In Western Electric Co. v. Baldwin International Radio of Canada, [1934] S.C.R. 570, the Court cited earlier authority dealing with the word "conduit" as used in a patent claim. Duff C.J. at p. 572 accepted the proposition that "[y]ou are not to look into the dictionary to see what 'conduit' means, but you are to look at the specification in order to see the sense in which the patentees have used it". In Consolboard, supra, as mentioned, Dickson J. considered that the whole of the specification (including the disclosure and the claims) should be looked at "to ascertain the nature of the invention" (p. 520). To the same effect is the statement of Taschereau J. in Metalliflex Ltd. v. Rodi & Wienenberger Aktiengesellschaft, [1961] S.C.R. 117, at p. 122:*
>
> > *The claims, of course, must be construed with reference to the entire specifications, and the latter may therefore be considered in order to assist in apprehending and construing a claim, but the patentee may not be allowed to expand his monopoly specifically expressed in the claims "by borrowing this or that gloss from other parts of the specifications".*
>
> *More recently, Hayhurst, supra, at p. 190, cautioned that "[t]erms must be read in context, and it is therefore unsafe in many instances to conclude that a term is plain and unambiguous without a careful review of the specification". In my view, it was perfectly permissible for the trial judge to look at the rest of the specification, including the drawing, to understand what was meant by the word "vane" in the claims, but not to enlarge or contract the scope of the claim as written and thus understood.*

[41] The Court may be assisted by expert witnesses in order to understand the context of the invention described and the particular meaning of terms used in the patent. The expert, however, is not to displace the Court in the role of the person who is to interpret the claims. In *Whirlpool* at paragraph 45 the Supreme Court stated:

> *45 The key to purposive construction is therefore the identification by the court, with the assistance of the skilled reader, of the particular words or phrases in the claims that describe what the inventor considered to be the "essential" elements of his invention. This is no different, I think, than the approach adopted roughly 40 years earlier by Duff C.J. in J. K. Smit & Sons, Inc. v. McClintock, [1940] S.C.R. 279. The patent in that case related to a method of setting diamonds in devices such as rotary drill bits for earth boring. Duff C.J., citing the earlier jurisprudence, put the focus on the inventor's own identification of the "essential" parts of his invention, at p. 285:*
>
> > *Obviously, the invention, as described by the inventor himself, involves the use of air suction to hold the diamonds in place while the molten metal is being introduced into the mold. There can be no doubt, in my mind, that as the inventor puts it, that is an essential part of his process. That part of his process is clearly not taken by the appellants. Adapting the language of Lord Romer, it is not the province of the court to guess what is and is not of the essence of the invention of the respondent. The patentee has clearly indicated that the use of air suction at that stage of the process is an essential, if not the essential, part of the invention described in the specification. [Emphasis added.]*

and at paragraph 57:

> *57 The third and most important obstacle to the appellants' dictionary approach is that it was not in fact consistent with the testimony of their own expert. The parties called three experts. The role of the expert was not to interpret the patent claims but to put the trial judge in the position of being able to do so in a knowledgeable way.*

6) Through Whose Eyes is Construction to be Made

[42] A patent is addressed to the "*ordinary person skilled in the art*" to which it pertains.

[43] In *Whirlpool* the Supreme Court said at paragraph 53:

> *"However, the patent specification is not addressed to grammarians, etymologists or to the public generally, but to skilled individuals sufficiently versed in the art to which the patent relates to enable them on a technical level to appreciate the nature and description of the invention."*

and at paragraph 53 the Court affirms that it is the "*ordinary*" worker skilled in the field who is to be regarded as the criterion:

> *53 A second difficulty with the appellants' dictionary approach is that it urges the Court to look at the words through the eyes of a grammarian or etymologist [page1099] rather than through the eyes and with the common knowledge of a worker of ordinary skill in the field to which the patent relates. An etymologist or grammarian might agree with the appellants that a vane of any type is still a vane. However, the patent specification is not addressed to grammarians, etymologists or to the public generally, but to skilled individuals sufficiently versed in the art to which the patent relates to enable them on a technical level to appreciate the nature and description of the invention: H. G. Fox, The Canadian Law and Practice Relating to Letters Patent for Inventions (4th ed. 1969), at p. 185. The court, writes Dr. Fox, at p. 203, must place itself*
>
> > *in the position of some person acquainted with the surrounding circumstances as to the state of the art and the manufacture at the time, and making itself acquainted with the technical meaning in that art or manufacture that any particular word or words may have.*
>
> *See also D. Vaver, Intellectual Property Law (1997), at p. 140. Knowledge of purpose is one of the important attributes the skilled worker brings to the exercise, as was made clear in Burton Parsons Chemicals, Inc. v. Hewlett-Packard (Canada) Ltd., [1976] 1 S.C.R. 555, a case that concerned the validity of a chemical patent. The invention was a type of conductive cream to be smeared on bits of the human body for the purpose of making electro-cardiograms and the like. The mixture was of no fixed composition. The essential invention was "to combine a highly ionizable salt with an aqueous emulsion" (p. 564). It was put in evidence that hundreds, if not thousands, of substances would fit the description, including some that would be toxic or irritating to the skin. A toxic "conductive cream" would not be a useful therapeutic tool, and it was alleged on that account that the patent lacked utility and was invalid. These objections were swept away by Pigeon J. who held that the notional skilled workman would understand perfectly well the purpose of the combination and could therefore be expected to apply the [page1100] teaching of the patent by sensibly choosing components suitable for that purpose (p. 563):*
>
> > *While the construction of a patent is for the Court, like that of any other legal document, it is however to be done on the basis that the addressee is a man skilled in the art and the knowledge such a man is expected to possess is to be taken into consideration. To such a man it must be obvious that a cream for use with skin contact electrodes is not to be made up with ingredients that are toxic or irritating, or are apt to stain or discolour the skin.*
>
> *Burton Parsons is a pre-Catnic instance of purposive construction where, as in Catnic itself, the skilled addressee made sense and purpose of the words used in the claim by deploying the common knowledge of someone in that position. It is through the eyes of such a person, not an etymologist or academic grammarian, that the terms of the specification, including the claims, must be read (Emphasis added).*

The same was stated by the Supreme Court at paragraph 44 of *Free World*:

> *44 The courts have traditionally protected a patentee from the effects of excessive literalism. The patent is not addressed to an ordinary member of the public, but to a worker skilled in the art described by Dr. Fox as*
>
> > *a hypothetical person possessing the ordinary skill and knowledge of the particular art to which the invention relates, and a mind willing to understand a specification that is addressed to him. This hypothetical person has sometimes been equated with the "reasonable man" used as a standard in negligence cases. He is assumed to be a man who is going to try to achieve success and not one who is looking for difficulties or seeking failure.*
> >
> > *(Fox, supra, at p. 184)*
>
> *It is the "common knowledge" shared by competent "ordinary workers" that is brought to bear on the interpretation: Fox, supra, at p. 204; Terrell on the Law of Patents (15th ed. 2000), at p. 125; I. Goldsmith, Patents of Invention (1981), at p. 116 (Emphasis added).*

[44] An "*ordinary*" worker was discussed by the Supreme Court at paragraphs 70 and 71 of *Whirlpool*. To encapsulate what was said, an "*ordinary*" worker is one who operates on the basis of common knowledge in the trade, possessing "*ordinary skills*" and not possessed with any special "*in house*" knowledge. At paragraph 74 the Court said:

> *"While the hypothetical "ordinary worker" is deemed to be uninventive as part of his fictional personality, he or she is thought to be reasonably diligent in keeping up with advances in the field to which the patent relates. The "common knowledge" of skilled workers undergoes continuous evolution and growth."*

7) What is to be Made of the Resulting Construction

[45] Purposive construction may be capable of expanding or limiting the literal text of the claim (*Whirlpool* paragraph 49(h)).

[46] It may be that the result is a "*self inflicted*" wound as stated in *Free World* paragraph 51:

> *51 This point is addressed more particularly in Whirlpool Corp. v. Camco Inc., [2000] 2 S.C.R. 1067, 2000 SCC 67 and Whirlpool Corp. v. Maytag Corp., [2000] 2 S.C.R. 1116, 2000 SCC 68, released concurrently. The involvement in claims construction of the skilled addressee holds out to the patentee the comfort that the claims will be read in light of the knowledge provided to the court by expert evidence on the technical meaning of the terms and concepts used in the claims. The words chosen by the inventor will be read in the sense the inventor is presumed to have intended, and in a way that is sympathetic to accomplishment of the inventor's purpose expressed or implicit in the text of the claims. However, if the inventor*

> *has misspoken or otherwise created an unnecessary or troublesome limitation in the claims, it is a self-inflicted wound. The public is [page1054] entitled to rely on the words used provided the words used are interpreted fairly and knowledgeably.*

[47] The public is entitled to a construction which, in the words used in paragraph 50 of *Free World* by the Supreme Court is "*in the interest of fairness both to the patentee and the public.*"

[48] Once a claim is construed, the Court may proceed to examine the issues of validity and infringement on the basis of that construction.

Throwing Up One's Hands - Ambiguity

[49] There is a temptation, particularly in hotly contested cases, to throw up one's hands and say that the claim is not capable of any construction, or any one construction. That is, it is ambiguous, therefore, invalid. The Supreme Court of Canada in *Pioneer Hi Bred* v. *Commissioner of Patents*, [1989] 1 S.C.R. 1623 has said at pages 1637 and 1638 :

> *In summary, the Patent Act requires that the applicant file a specification including disclosure and claims (Consolboard Inc., supra, at p. 520). Canadian courts have stated in a number of cases the test to be applied in determining whether [page1638] disclosure is complete. The applicant must disclose everything that is essential for the invention to function properly. To be complete, it must meet two conditions: it must describe the invention and define the way it is produced or built*
>
> ***
>
> *The applicant must define the nature of the invention and describe how it is put into operation. A failure to meet the first condition would invalidate the application for ambiguity, while a failure to meet the second invalidates it for insufficiency. The description must be such as to enable a person skilled in the art or the field of the invention to produce it using only the instructions contained in the disclosure*
>
> ***
>
> *and once the monopoly period is over, to use the invention as successfully as the inventor could at the time of his application.*

[50] Section 36(2) requires that a patent end with claims that "*clearly and distinctly*" describe the invention.

[51] The last time a Canadian court held a claim to be ambiguous, hence invalid, was in addressing one of many patents at issue in *Xerox of Canada Ltd.* v. *IBM Canada Ltd.* (1977), 33 C.P.R. (2nd) 24 at pages 82-83. In retrospect today's Court may simply have held the claim not to be infringed. Prior to that one must go back to the early 1930's where the Supreme Court of Canada in *Complex Ore Reduction Co.* v. *Electrolytic Zinc Process Co.* [1930] S.C.R. 462 held a patent to be invalid for ambiguity. At pages 475 and 476 Rinfret J. said:

> *To sum up our views, on this branch of the case, we think the specification is insufficient. It fails to comply with the conditions of clarity and distinctness required by section 13 of the Act and does not state in precise and unambiguous terms in what the alleged invention consists. If the descriptive part of the specification be construed as suggested by counsel for the French Company, the claims were not made to conform with it and they are inadequate for that purpose. We can find in the patent no other subject-matter patentable in law. The utility or the beneficial effect of manganese or of certain proportions of manganese are not what French*
>
> > *claimed as new and for the use of which he claimed an exclusive property and privilege.*
>
> *At least, he did not clearly and distinctly do so. In the words of Fletcher Moulton L.J., the claim is*
>
> > *a separate part of the specification primarily designed for delimitation.*
>
> *British United Shoe Machinery Company Limited v. A. Fussel & Sons, Limited [(1908) 25 R.P.C. 631 at p. 650.]. The delimitation must be clearly marked out. And, in conclusion, we will quote the following passage from Lord Halsbury's speech in The British Ore Concentration Syndicate Limited v. Minerals Separation Limited [(1909) 27 R.P.C. 33, at p. 47.].*
>
> > *The statute requires it (the specification) to be a distinct statement of what is the invention. In construing a specification one has to remember that it is a document not only assuring a monopoly to the patentee, which but for the statute would be contrary to the common law, but so (also?) prohibiting any one, other than the patentee, doing what he would be free to do, but for the right which is granted, subject to the condition, among other things, that the patentee states distinctly what his invention is. If he designedly makes it ambiguous, in my judgment the patent would undoubtedly be bad on that ground; but even if negligently and unskilfully he fails to make distinct what his invention is, I am of opinion that the condition is not fulfilled,*

and the consequence would be that the patent would be bad."

[52] As a practical matter, Canadian courts have resisted holding claims to be incapable of meaning. The modern approach is exemplified by Mosley J. in *Letourneau* v. *Clearbrook Iron Works Ltd.*, September 26, 2005, 2005 F.C. 1229 at paragraphs 37 and 38:

> *[37] A claim is not invalid simply because it is not a model of concision and lucidity. Very few patent claims are. Claims are drafted to be understood by people with practical knowledge and experience in the specific field of the invention: Risi Stone Ltd.supra, at 20. If a term can be interpreted using grammatical rules and common sense, it cannot be ambiguous: Mobil Oil Corp. v. Hercules Canada Inc. (1995), 63 C.P.R (3d) 473 at 484, 188 N.R. 382 (F.C.A.).*
>
> *[38] The Court must give a purposive construction to a claim without being too astute or technical. If there is more than one construction that can be reasonably reached, the Court must favour the construction which upholds the patent. Where the language of the specification, upon a reasonable view of it, can be read so as to afford the inventor protection for that which he has actually in good faith invented, the court, as a rule, will endeavour to give effect to that construction: Lubrizol Corp. v. Imperial Oil Ltd. (1992), 45 CPR (3d) 449, 98 D.L.R. (4th) 1 (F.C.A.); Western Electric Co. Inc. and Northern Electric Co. v. Baldwin International Radio of Canada Ltd., [1934] S.C.R. 570, [1934] 4 D.L.R. 129; Unilever PLC. v. Proctor & Gamble Inc., [1995] F.C.J. No. 1005 at para 23, 61 C.P.R. (3d) 499 (F.C.A.).*

[53] In short, ambiguity is truly a last resort, rarely, if ever, to be used.

Construction of the Claim(s) at Issue

[54] The parties are agreed that claim 1 typifies all claims for the purposes of construction. To re-iterate, it reads:

> *An injectable, ready-to-use, sterile, pyrogen-free, anthracycline glycoside solution which consists essentially of a physiologically acceptable salt of an anthracycline glycoside dissolved in a physiologically acceptable aqueous solvent therefore at an anthracycline glycoside concentration of from 0.1 to 50 mg/ml, which has not been reconstituted from a lyophilizate and the pH of which has been adjusted to from 2.5 to 5.0 solely with a physiologically acceptable acid.*

Or, with most of the technical terms removed:

> *An injectable, ready-to-use solution which consists essentially of a salt of the active ingredient dissolved in an acceptable solvent at a given range of concentration, which has not been*

reconstituted from a lyophilizate and the pH of which has been adjusted to a certain range solely with an acceptable acid.

[55] The issue for resolution is to what does the phrase "*which has not been reconstituted from a lyophizate*" refer? Does it refer to the "*ready-to-use solution*" or to the "*acceptable salt.*"

[56] I will refer to the rules of construction set out previously.

1. Who constitutes the claim?

[57] This Court construes the claims. Statements made by the experts, such as Beijnen at paragraph 59 and Cunningham at paragraph 24 are to be given no weight when it comes to construction.

2. When are the claims to be construed?

[58] The claims are to be construed now, before considering infringement. Validity is not at issue in these proceedings.

3. As of what date is the patent to be construed?

[59] This is an "*old*" *Act* patent. It is to be construed as of the date that it was issued and granted - October 22, 1991.

4. What are the criteria for construction?

[60] The claim is to be read in the context of the specification, against the background of the state of the art as set out as it existed as of the date upon which the claims is to be construed.

5. What resources may be used for construction

[61] The evidence of the experts may be used as background against which the description contained in the specification is to be read in arriving at a purposive construction of the claims.

6. Through Whose eyes is construction to be made?

[62] Through the eyes of an ordinary person skilled in the art. Certainly Beijnen meets this criteria. Cunningham is more of a generalist, however his comments are useful. Murgatroyd speaks only to the chemistry of lyophilization and to that limited extent, his comments are useful.

Therefore – Construing the Claim

[63] As to the state of this art, the evidence of the expert offered by Pfizer, Beijnen, and those offered by Mayne, Cunningham and Murgatroyd, were, by and large, not in conflict. Beijnen was more experienced in the particular field and offers greater assistance when it comes to what the background was that existed as of the relevant time, October 1991. The evidence as to the background is:

1. Lyophilization, in layman's terms freeze-drying, was a common technique applied to a variety of substances including certain medicines in order that they may be stored for a period of time and remain stable. (Beijnen paragraphs 15 and 16, Cunningham paragraph 19, Murgatroyd paragraphs 14 and 15).

2. A "*lyophilizate*" is the product of lyophilization (Beijnen paragraph 15, Cunningham paragraph 27).

3. With respect to the chemical at issue anthracycline glycocide and,in particular doxorubicin, it was commercially available as a salt only in a lyophilized form (Beijnen paragraphs 14 and 17 and Beijnen cross examination page 72 line 22 to page 73 line 7, Exhibit 2).

4. Anthracycline glycocides and in particular doxorubicin were extremely toxic. Exposure to humans whether during manufacture or in preparation for administration to a patient could be very harmful (Beijnen paragraphs 19 to 24, Cunningham paragraphs 37 to 39, Cunningham cross examination page 90 line 21 to page 97 line 11).

5. Anthracycline glycocides were useful in the treatment of certain cancers (Beijnen paragraph 12).

6. In the medical use context anthracycline glycocides and in particular doxorubicin were presented to a nurse or, other person administering the drug to a patient, in the form of a lyophilized material mixed with excipients such as lactose, contained in a sealed vial. The stopper of the vial would be punctured and a solvent such as water introduced. The vial was shaken until the material went into solution. A second puncture was made through the stopper into the vial and the solution was administered to a patient. Care

needed to be taken by the nurse or other such person, to avoid exposure to the material in the vial (Beijnen paragraph 20).

[64] Against this background, the specification of the '037 may be read. The background of the invention is set out at pages 1 and 2 which can be abridged as follows:

> *The present invention related to a stable intravenously injectable ready-to-use solution of an antitumor anthracycline glycoside, e.g. doxorubicin, to a process for preparing such a solution, and provide the same in a sealed container and to a method for treating tumors by the use of the said ready-to-use solution.*
>
> *The anthracycline glycoside compounds are a well known class of compounds in the antineoplastic group of agents, wherein doxorubicin is a typical, and the most widely used, representative.*
>
> ***
>
> *At present, anthracycline glycoside antitumor drugs, in particular, e.g. doxorubicin, are solely available in the form of lyophilized preparations, which need to be reconstituted before administration.*
>
> *Both the manufacturing and the reconstitution of such preparations expose the involved personnel (workers, pharmacists, medical personnel, nurses) to risks of contamination which are particularly serious due to the toxicity of the antitumor substances.*
>
> *The Martindale Extra Pharmacopoeia 28th edition, page 175 left column, reports, indeed, about adverse effects of antineaplastic drugs and recommends that "They must be handled with great care and contact with skin and eyes avoided, they should not be inhaled. Care must be taken to avoid extranvasation since pain and tissue damage may ensue."*
>
> ***
>
> *Similarly, report about severe adverse effects observed in medical personnel exposed to use of cytostatic agents, including doxorubicin.*
>
> *To administer a lyophilized preparation, double handling of the drug is required, the lyophilized cake having to be first reconstituted and then administered and, moreover, in some cases, the complete dissolution of the powder may require prolonged shaking because of solubilization problems.*
>
> *As the risks connected with the manufacturing and the reconstitution of a lyophilized preparate would be highly reduced if a ready-to-use solution of the drug were available, we have developed a stable, therapeutically acceptable intravenously injectable solution of an anthracycline glycoside drug, e.g. doxorubicin, whose preparation and administration does not require either lyophilization or reconstitution.*

[65] The invention is stated at pages 3 to 9 starting with a statement which is simply a recitation of what is contained in claim 1 followed by a number of examples and choices which are set out for each of the ingredients and parameters. Other ingredients if desired are indicated.

[66] The resulting advantage is set out at page 9.

> *With the solutions of the invention it is possible to obtain compositions having a very high concentration of the anthracycline glycoside active substance even at 50 mg/ml. This constitutes a great advantage over the presently available lyophilized preparate wherein high concentrations of anthracycline glycoside can only be obtained with difficulty because of solubilization problems encountered in reconstitution, mainly with saline. The presence of the excipient, e.g. lactose, in the lyophilized cake, and its generally high proportion in respect of the active substance, even up to 5 parts of excipient per part of active substance, has a negative effect on solubilization so that difficulties may arise in obtaining dissolution of the lyophilized cake.*

[67] A process for making such solutions is described at page 8 in which, after stating that the solution to be made is as set out in claim 1, it says:

> *"... which process comprises dissolving the said physrotogically (SP) acceptable salt, which salt is not in the form of a lyophilizate, in the said solvent..."*

[68] This process description, says Mayne, means that the phrase in claim 1 "*which has not been reconstituted from a lyophilizate*" is directed to the salt, not the solution. Pfizer says that this statement in the process is directed to the avoidance of undue exposure during the manufacture stage and that the process as described is only one of several processes that could be used.

[69] Mayne further argues, after scouring the description for all uses of lyophilizate or lyophilized cake or lyophilized preparation or lyophilized preparate or freeze-dried preparate, that the word lyophilizate meant only the salt. Pfizer says that lyophilizate means anything that contains lyophilized active ingredient.

[70] These exercises engaged in by counsel for Pfizer and Mayne are precisely the exercises that the Supreme Court says one is to avoid. One avoids a "*grammatical*" or "*etymological*" approach. One looks at the claim in light of the specification against the background in September 1991 as it would be understood by an ordinary person skilled in the art.

[71] An ordinary person skilled in the art would understand that the invention was to deliver to the public something that it did not have before namely, a ready-to-use, stable preparation of the medicine in a form that did not require reconstitution from a powder, by the nurse of other person administering the drug. In this context the phrase "*which has not been reconstituted from a lyophilizate*" can only refer to the solution and not one of its ingredients, the salt.

7. What is the result?

[72] In the result, Pfizer's construction of the claims is the correct one. On that construction the Mayne product is an infringement of at least claim 1.

[73] Therefore, Mayne's allegation as to non-infringement is not justified and the Minister will be prohibited from issuing to Mayne a Notice of Compliance in respect of its application at issue here.

Adequacy of the Notice of Allegation

[74] Pfizer, in its Notice of Application, alleged that Mayne's Notice of Allegation was inadequate. Very little was made of this at the hearing and the point, except for a small querulous

point made in reply, was abandoned by Pfizer. Certainly no evidence was led by Pfizer to the effect that they were puzzled or misled.

[75] Such a plea has become somewhat commonplace in these NOC proceedings and should only be made where truly it is justified.

[76] Where experienced parties with experienced Counsel proceed in such matters without a proper demonstration to the Court as to true inadequacy of the Notice of Allegation, such a plea should not stand (*Aventis Pharma Inc.* v. *Apotex Inc.*, 2005 F.C. 1283 at paras. 98-108; *Aventis Pharma Inc.* v. *Apotex Inc.*, 2005 F.C. 1504 at paras 48-50).

[77] Here the plea of inadequacy has not been made out and should be dismissed with a cost penalty to dissuade such pleading by others in the future. I propose, at this time, a modest one-quarter deduction from costs otherwise allowed.

Costs

[78] Counsel have asked that I reserve as to the matter of costs until after this judgment has been released and considered by them. I propose therefore, that counsel shall have ten (10) working days from release of this judgement to provide written submissions as to costs. Those submissions are to be guided by the following considerations:

1. Pfizer was successful and, in the normal course, would be entitled to its costs;

2. Pfizer's costs should be reduced by one-quarter as previously indicated;

3. The proceedings were, as almost all NOC proceedings, hard fought and requiring of good skills. They were not, however, exceptional and the high end of Column III may be appropriate;

4. The expert Beijnen should be allowed his fees and disbursements. However, the Court is concerned with escalating expert fees in general and suggest that such fees should not exceed those allowed for lead counsel in preparing for and arguing the case;

5. Pfizer had three counsel gowned, Mayne had one. The Pfizer case could have been argued by one counsel only.

6. Cross-examinations were conducted overseas. Modest, not extravagant, disbursements should be allowed.

In Conclusion

[79] An order will go in the following terms:

1. The Minister of Health is prohibited from issuing a Notice of Compliance to Mayne Pharma (Canada) Inc. in respect of Epirubicin Hydrochloride Injection Ph. Eur. Having a strength per dosage unit of 2 mg/ml until the expiry of Canadian Letters Patent on

October 22, 2008 or earlier if said patent is held to be invalid by an unappealable judgment of a competent Canadian Court; and

2. Counsel shall provide written submissions as to costs within ten (10) working days from the date hereof following which a further Order as to costs will be made.

"Roger T. Hughes"

JUDGE

Toronto, Ontario
December 20, 2005

FEDERAL COURT

NAMES OF COUNSEL AND SOLICITORS OF RECORD

DOCKET:	T-1142-04
STYLE OF CAUSE:	PFIZER CANADA INC. and PHARMACIA ITALIA S.p.A. Applicants and THE MINISTER OF HEALTH and MAYNE PHARMA (CANADA) INC. Respondents
PLACE OF HEARING:	TORONTO, ONTARIO
DATE OF HEARING:	DECEMBER 12 & 13, 2005
REASONS FOR ORDER:	HUGHES J.
DATED:	DECEMBER 20, 2005

APPEARANCES:

Sheila Block Kameleh Nicola Cynthia L. Tape	FOR APPLICANTS
Susan D. Beaubien	FOR RESPONDENTS

SOLICITORS OF RECORD:

Torys LLP Toronto, Ontario	FOR APPLICANTS
Susan D. Beaubien Barrister & Solicitor Ottawa, Ontario	FOR RESPONDENTS

JS 44
(Rev. 12/96)

CIVIL COVER SHEET

The JS-44 civil cover sheet and the information contained herin neither replace nor supplement the filing and service of pleadings or other papers as required by law, except as provided by local rules of court. This form, approved by the Judicial Conference of the United States in September 1974, is required for the use of the Clerk of Court for the purpose of initiating the civl docket sheet. (SEE INSTRUCTIONS ON THE REVERSE OF THE FORM.)

I. (a) PLAINTIFF

PHARMACIA & UPJOHN COMPANY LLC

(b) COUNTY OF RESIDENCE OF FIRST LISTED PLAINTIFF _____
(EXCEPT IN U.S. PLAINTIFF CASES)

DEFENDANT

MAYNE PHARMA (USA) INC.

COUNTY OF RESIDENCE OF FIRST LISTED DEFENDANT _____
(IN U.S. PLAINTIFF CASES ONLY)
NOTE: IN LAND CONDEMNATION CASES, USE THE LOCATION OF THE TRACT OF LAND INVOLVED.

(c) ATTORNEYS (FIRM ADDRESS AND TELEPHONE NUMBER)
Jack B. Blumenfeld (#1014)
Maryellen Noreika (#3208)
Morris, Nichols, Arsht & Tunnell LLP
1201 N. Market Street
P.O. Box 1347
Wilmington, DE 19801
302-658-9200

ATTORNEYS (IF KNOWN)

II. BASIS OF JURISDICTION (PLACE AN "X" IN ONE BOX ONLY)

- ☐ 1 U.S. Government Plaintiff
- ☒ 3 Federal Question (U.S. Government Not a Party)
- ☐ 2 U.S. Government Defendant
- ☐ 4 Diversity (Indicate Citizenship of Parties in Item III)

III. CITIZENSHIP OF PRINCIPAL PARTIES
(For Diversity Cases Only)

(PLACE AN "X" IN ONE BOX FOR PLAINTIFF AND ONE BOX FOR DEFENDANT)

	PTF	DEF		PTF	DEF
Citizen of This State	☐ 1	☐ 1	Incorporated or Principal Place of Business in This State	☐ 4	☐ 4
Citizen of Another State	☐ 2	☐ 2	Incorporated and Principal Place of Business in Another State	☐ 5	☐ 5
Citizen or Subject of a Foreign Country	☐ 3	☐ 3	Foreign Nation	☐ 6	☐ 6

IV. ORIGIN *(PLACE AN "X" IN ONE BOX ONLY)*

☒ 1 Original Proceeding | ☐ 2 Removed From State Court | ☐ 3 Remanded From Appellate Court | ☐ 4 Reinstated or Reopened | ☐ 5 Transferred From another district (specify) _____ | ☐ 6 Multidistrict Litigation | ☐ 7 Appeal to District Judge from Magistrate Judgement

V. NATURE OF SUIT *(PLACE AN "X" IN ONE BOX ONLY)*

CONTRACT
- ☐ 110 Insurance
- ☐ 120 Marine
- ☐ 130 Miller Act
- ☐ 140 Negotiable Instrument
- ☐ 150 Recovery of Overpayment & Enforcement of Judgement
- ☐ 151 Medicare Act
- ☐ 152 Recovery of Defaulted Student Loans (Excl Veterans)
- ☐ 153 Recovery of Overpayment of Veteran's Benefits
- ☐ 160 Stockholder Suits
- ☐ 190 Other Contract
- ☐ 195 Contract Product Liability

REAL PROPERTY
- ☐ 210 Land Condemnation
- ☐ 220 Foreclosure
- ☐ 230 Rent Lease & Ejectment
- ☐ 240 Torts to Land
- ☐ 245 Tort Product Liability
- ☐ 290 All Other Real Property

TORTS

PERSONAL INJURY
- ☐ 310 Airplane
- ☐ 315 Airplane Product Liability
- ☐ 320 Assault Libel & Slander
- ☐ 330 Federal Employers Liability
- ☐ 340 Marine
- ☐ 345 Marine Product Liability
- ☐ 350 Motor Vehicle
- ☐ 355 Motor Vehicle Product Liability
- ☐ 360 Other Personal Injury

PERSONAL INJURY
- ☐ 362 Personal Injury - Med Malpractice
- ☐ 365 Personal Injury - Product Liability
- ☐ 368 Asbestos Personal Injury Product Liability

PERSONAL PROPERTY
- ☐ 370 Other Fraud
- ☐ 371 Truth in Lending
- ☐ 380 Other Personal Property Damage
- ☐ 385 Property Damage Product Liability

CIVIL RIGHTS
- ☐ 441 Voting
- ☐ 442 Employment
- ☐ 443 Housing/ Accommodations
- ☐ 444 Welfare
- ☐ 440 Other Civil Rights

PRISONER PETITIONS
- ☐ 510 Motions to Vacate Sentence

HABEAS CORPUS:
- ☐ 530 General
- ☐ 535 Death Penalty
- ☐ 540 Mandamus & Other
- ☐ 550 Civil Rights
- ☐ 555 Prison Condition

FORFEITURE/PENALTY
- ☐ 610 Agriculture
- ☐ 620 Other Food & Drug
- ☐ 625 Drug Related Seizure of Property 21 USC 881
- ☐ 630 Liquor Laws
- ☐ 640 R R & Truck
- ☐ 650 Airline Regs
- ☐ 660 Occupational Safety/Health
- ☐ 690 Other

LABOR
- ☐ 710 Fair Labor Standards Act
- ☐ 720 Labor/Mgmt. Relations
- ☐ 730 Labor Mgmt. Reporting & Disclosure Act
- ☐ 740 Railway Labor Act
- ☐ 790 Other Lablor Litigation
- ☐ 791 Empl Ret Inc Security Act

BANKRUPTCY
- ☐ 422 Appeal 28 USC 158
- ☐ 423 Withdrawal 28 USC 157

PROPERTY RIGHTS
- ☐ 820 Copyrights
- ☒ 830 Patent
- ☐ 840 Trademark

SOCIAL SECURITY
- ☐ 861 HIA (1395ff)
- ☐ 862 Black Lung (923)
- ☐ 863 DIWC/DIWW (405(g))
- ☐ 864 SSID Title XVI
- ☐ 865 RSI (405(g))

FEDERAL TAX SUITS
- ☐ 870 Taxes (U.S. Plaintiff or Defendant
- ☐ 871 IRS - Third Party 26 USC 7609

OTHER STATUTES
- ☐ 400 State Reapportionment
- ☐ 410 Antitrust
- ☐ 430 Banks or Banking
- ☐ 450 Commerce/ICC Rates/etc
- ☐ 460 Deportation
- ☐ 470 Racketeer Influenced and Corrupt Organizations
- ☐ 810 Selective Service
- ☐ 850 Securities/Commodities/ Exchange
- ☐ 875 Customer Challenge 12 USC 3410
- ☐ 891 Agricultural Acts
- ☐ 892 Economic Stabilization Act
- ☐ 893 Environmental Matters
- ☐ 894 Energy Allocation Act
- ☐ 895 Freedom of Information Act
- ☐ 900 Appeal of Fee Determination Under Equal Access to Justice
- ☐ 950 Constitutionality of State Statutes
- ☐ 890 Other Statutory Actions

VI. CAUSE OF ACTION (CITE THE U.S. CIVIL STATUTE UNDER WHICH YOU ARE FILING AND WRITE BRIEF STATEMENT OF CAUSE DO NOT CITE JURISDICTIONAL STATUTES UNLESS DIVERSITY)

Patent infringement under 35 U.S.C. § 271

VII. REQUESTED IN COMPLAINT

☐ CHECK IF THIS IS A **CLASS ACTION** UNDER F.R.C.P. 23

DEMAND $

CHECK YES only if demanded in complaint:
JURY DEMAND: ☐ YES ☒ NO

VIII. RELATED CASE(S) IF ANY (See Instructions) Pharmacia & Upjohn Company LLC v. Sicor Inc. and Sicor Pharmaceuticals, Inc.

JUDGE Kent A. Jordan DOCKET NUMBER 04-833 (KAJ)

DATE 9/7/06

SIGNATURE OF ATTORNEY OF RECORD

FOR OFFICE USE ONLY

RECEIPT # _____ AMOUNT _____ APPLYING IFP _____ JUDGE _____ MAG. JUDGE _____

AO FORM 85 RECEIPT (REV. 9/04)

United States District Court for the District of Delaware

Civil Action No. 06-554

ACKNOWLEDGMENT OF RECEIPT FOR AO FORM 85

NOTICE OF AVAILABILITY OF A UNITED STATES MAGISTRATE JUDGE TO EXERCISE JURISDICTION

I HEREBY ACKNOWLEDGE RECEIPT OF 2 COPIES OF AO FORM 85.

9/7/2006
(Date forms issued)

(Signature of Party or their Representative)

Aaron Johnston
(Printed name of Party or their Representative)

Note: Completed receipt will be filed in the Civil Action